Rec'd PCT/PTO 27 MAR 2001

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TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 01056

U.S APPLICATION NO. (If known, see 37 CFR 1.5): 09/787436

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/07389	September 23, 1999	September 30, 1998

TITLE OF INVENTION: PHARMACEUTICAL COMPOSITIONS BASED ON ALPHA-CYCLODEXTRIN FOR THE ORAL ADMINISTRATION OF LH-RH ANALOGUES

APPLICANT(S) FOR DO/EO/US: Remi DELANSORNE; Paule BONNET; and Jacques PARIS

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)).
4. [ ] The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is attached hereto (required only if not communicated by the International Bureau).
   b. [X] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 16 below concern document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [X] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [ ] Other items or information:

U.S. APPLICATION NO (if known, see 37 CFR 1.5) 09/787436	INTERNATIONAL APPLICATION NO PCT/EP00/07389	ATTORNEY'S DOCKET NUMBER 01056

17 [X] The following fees are submitted:	CALCULATIONS PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :	
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**	
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**	

ENTER APPROPRIATE BASIC FEE AMOUNT =				$ 860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				$	
CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE	
Total claims	58	- 20 =	38	X $18.00	$ 684.00
Independent claims	3	- 3 =	0	X $80.00	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+ $270.00	$
TOTAL OF ABOVE CALCULATIONS =					$ 1,544.00
[ ] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.					$
SUBTOTAL =					$ 1,544.00
Processing fee of **$130.00** for furnishing the English translation later than [ ]20 [ ]30 months from the earliest claimed priority date (37 CFR 1.492(f)). +					$
TOTAL NATIONAL FEE =					$ 1,544.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +					$ 40.00
TOTAL FEES ENCLOSED =					$ 1,584.00
				Amount to be refunded:	$
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a. [ ] A check in the amount of $_____ to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 04-0753. A duplicate copy of this sheet is enclosed.

d. [X] A payment of $1,584.00 is made by credit card. A Credit Card Payment Form (PTO-2038) is attached hereto. The Commissioner is hereby authorized to charge payment of any additional filing fees required under 37 CFR 1.16 or any patent application processing fees under 37 CFR 1.17, or credit any over payment to the credit card account shown on the attached Credit Card Payment Form. Refund of all amounts overpaid, including those of twenty-five dollars or less, is specifically requested.

SEND ALL CORRESPONDENCE TO:
Dennison, Scheiner, Schultz & Wakeman
612 Crystal Square 4
1745 Jefferson Davis Highway
Arlington, VA 22202-3417
Telephone (703) 412-1155 Ext.
Facsimile (703) 412-1161

SIGNATURE

Ira J. Schultz
NAME

28666
REGISTRATION NUMBER

09/787436

01056

JC08 Rec'd PCT/PTO 27 MAR 2001

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE: APPLICATION OF: :

Rémi DELANSORNE ET AL :

NATIONAL STAGE OF PCT/EP99/07389 :

FILED: CONCURRENTLY HEREWITH :

FOR: PHARMACEUTICAL COMPOSITIONS BASED ON ALPHA-CYCLODEXTRIN FOR THE ORAL ADMINISTRATION OF LH-RH ANALOGUES

PRELIMINARY AMENDMENT
and
INFORMATION DISCLOSURE STATEMENT

ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

Sir,

Before calculation of the filing fee, kindly amend the above-identified application as follows.

IN THE SPECIFICATION

Page 1, immediately below the Title, insert the paragraph --This application is a 371 of PCT/EP99/07389, filed September 23, 1999.--

LAW OFFICES
DENNISON, SCHEINER, SCHULTZ & WAKEMAN
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155

Please insert the attached Sequence Listing immediately before the Claims.

IN THE CLAIMS

Please amend the claims as follows (including Claims 35-62 attached to the International Preliminary Examination Report):

Cancel claims 1-20 without prejudice or disclaimer to the subject matter thereof.

Amend Claims 23, 28, 31-34, 41, 44-45, 52, 55-56, 58, 60 and 62 as follows:

23. (Amended) The pharmaceutical composition according to claim 21 wherein said peptide analogue has the formula (SEQ ID N° : 1) :

A1-A2-A3-A4-A5-A6-A7-A8-Pro-Z(A)

in which :

- A1 is pGlu ; D-pGlu ; Sar ; AcSar ; Pro or a derivative thereof ; Ser ; D-Ser ; Ac-D-Ser ; Thr ; D-Thr ; Ac-D-Thr ; or an aromatic D-amino acid which may be acylated ;
- A2 is a direct bond ; His ; or an aromatic D-amino acid;
- A3 is an aromatic L- or D-amino acid;
- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;

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- A5 is an aromatic L-amino acid ; or a basic L- or D-amino acid;

- A6 is Gly ; (S)-spirolactam-Pro ; D-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t) ; D-Ser(OR_1) where R_1 is a sugar moiety ; an aza-amino acid ; D-His which may be substituted on the imidazole ring by a (C_1-C_6)alkyl, a (C_2-C_7)acyl or a benzyl group ; an aliphatic D-amino acid with a (C_1-C_8)alkyl or a (C_3-C_6)cycloalkyl side chain ; an aromatic D-amino acid ; D-cyclohexadienyl-Gly ; D-perhydronaphthyl-Ala ; D-perhydrodiphenyl-Ala ; or a basic L- or D-amino acid;

- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C_1-C_4)alkyl group optionally substituted by one or several fluorine atoms;

- A8 is a basic L- or D-amino acid ;

- Z is $GlyNH_2$; D-$AlaNH_2$; aza$GlyNH_2$; or a group $-NHR_2$ where R_2 is a (C_1-C_4)alkyl which may be substituted by an hydroxy or one or several fluorine atoms ; a (C_3-C_6)cycloalkyl ; or a

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heterocyclic radical selected from morpholinyl, pyrrolidinyl and piperidyl.

28. (Amended) The pharmaceutical composition according to claim 24 wherein the peptide analogue is selected from the group consisting of leuprorelin, [Npg^7]-leuprorelin, triptorelin, [Npg^7]-triptorelin, goserelin, [Npg^7]-goserelin, buserelin and [Npg^7]-buserelin.

31. (Amended) The pharmaceutical composition according to claim 29 wherein the peptide analogue is selected from the group consisting of antide, [Npg^7]-antide, cetrorelix, [Npg^7]-cetrorelix, abarelix and [Npg^7]-abarelix.

32. (Amended) The pharmaceutical composition according to claim 21 wherein the α-cyclodextrin derivative is selected from the group consisting of methylated α-cyclodextrin, hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin, carboxy-methylated α-cyclodextrin and phosphated α-cyclodextrin.

33. (Amended) The pharmaceutical composition according to claim 32 wherein the α-cyclodextrin derivative is hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin.

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34. (Amended) The pharmaceutical composition according to claim 21 which further comprises a compound selected from the group consisting of a protease inhibitor, an absorption enhancer, and mixtures thereof.

41. (Amended) The method according to claim 37 wherein the peptide analogue is selected from the group consisting of leuprorelin, [Npg^7]-leuprorelin, triptorelin, [Npg^7]-triptorelin, goserelin, [Npg^7]-goserelin, buserelin and [Npg^7]-buserelin.

44. (Amended) The method according to claim 42 wherein the peptide analogue is selected from the group consisting of antide, [Npg^7]-antide, cetrorelix, [Npg^7]-cetrorelix, abarelix and [Npg^7]-abarelix.

45. (Amended) The method according to claim 35 wherein the α-cyclodextrin derivative is selected from the group consisting of methylated α-cyclodextrin, hexakis(2,3,6-tri-O-methyl)- α-cyclodextrin, carboxymethylated α-cyclodextrin and phosphated α-cyclodextrin.

52. (Amended) The method according to claim 48 wherein the peptide analogue is selected from the group consisting of

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leuprorelin, [Npg^7]-leuprorelin, triptorelin, [Npg^7]-triptorelin, goserelin, [Npg^7]-goserelin, buserelin and [Npg^7]-buserelin.

55. (Amended) The method according to claim 53 wherein the peptide analogue is selected from the group consisting of antide, [Npg^7]-antide, cetrorelix, [Npg^7]-cetrorelix, abarelix and [Npg^7]-abarelix.

56. (Amended) The method according to claim 47 wherein the α-cyclodextrin derivative is selected from the group consisting of methylated α-cyclodextrin, hexakis(2,3,6-tri-O-methyl)- α-cyclodextrin, carboxymethylated α-cyclodextrin and phosphated α-cyclodextrin.

58. (Amended) The method according to claim 47 for the treatment or prevention of breast cancer.

60. (Amended) The method according to claim 47 for the treatment or prevention of prostate cancer or benign prostatic hypertrophy.

62. (Amended) The method according to claim 47 wherein the peptide analogue is delivered to the gastrointestinal tract of the patient.

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Please add the following new claims:

--63. (New) The pharmaceutical composition according to claim 28 wherein the α-cyclodextrin derivative is selected from the group consisting of methylated α-cyclodextrin, hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin, carboxy-methylated α-cyclodextrin and phosphated α-cyclodextrin.

64. (New) The pharmaceutical composition according to claim 28 comprising α-cyclodextrin or hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin.

65. (New) The pharmaceutical composition according to claim 64 wherein the peptide analogue is leuprorelin.

66. (New) The pharmaceutical composition according to claim 64 wherein the peptide analogue is [Npg^7]-leuprorelin.

67. (New) The method according to claim 41 wherein the α-cyclodextrin derivative is selected from the group consisting of methylated α-cyclodextrin, hexakis(2,3,6-tri-O-methyl)- α-cyclodextrin, carboxymethylated α-cyclodextrin and phosphated α-cyclodextrin.

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68. (New) The method according to claim 67 wherein the α-cyclodextrin derivative is hexakis(2,3,6-tri-O-methyl)- α-cyclodextrin.

69. (New) The method according to claim 35, which comprises orally administering a therapeutically effective amount of leuprorelin in combination with α-cyclodextrin or hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin.

70. (New) The method according to claim 35, which comprises orally administering a therapeutically effective amount of [Npg^7]-leuprorelin in combination with α-cyclodextrin or hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin.

71. (New) The method according to claim 52 wherein the α-cyclodextrin derivative is selected from the group consisting of methylated α-cyclodextrin, hexakis(2,3,6-tri-O-methyl)- α-cyclodextrin, carboxymethylated α-cyclodextrin and phosphated α-cyclodextrin.

72. (New) The method according to claim 71 wherein the α-cyclodextrin derivative is hexakis(2,3,6-tri-O-methyl)- α-cyclodextrin.

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73. (New) The method according to claim 47, which comprises orally administering a therapeutically effective amount of leuprorelin in combination with α-cyclodextrin or hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin.

74. (New) The method according to claim 47, which comprises orally administering a therapeutically effective amount of [Npg^7]-leuprorelin in combination with α-cyclodextrin or hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin.

75. (New) The method according to claim 62 wherein the α-cyclodextrin derivative is selected from the group consisting of methylated α-cyclodextrin, hexakis(2,3,6-tri-O-methyl)- α-cyclodextrin, carboxymethylated α-cyclodextrin and phosphated α-cyclodextrin.

76. (New) The method according to claim 71 wherein the α-cyclodextrin derivative is hexakis(2,3,6-tri-O-methyl)- α-cyclodextrin.

77. (New) The method according to claim 76 wherein the peptide analogue is leuprorelin.

78. (New) The method according to claim 76 wherein the peptide analogue is [Npg^7]-leuprorelin.--

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612 CRYSTAL SQUARE 4
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SUPPORT FOR THE AMENDMENT

Support for new claims 63-78 is found on pages 2-18 of the specification and in the original claims.

REMARKS

Claims 21-78 are presented for initial examination.

The claims have been amended to eliminate all multiple dependencies (Claims 23, 28, 31-34, 41, 44-45, 52, 55-56, 58, 60 and 62) and to provide conventional Markush language (Claim 34). No new matter is believed to be added to the application by entry of these amendments. None of the amendments to the claims are believed to be a narrowing of the claims and, accordingly, should not limit interpretation of the claims under the Doctrine of Equivalents.

A written paper copy of the Sequence Listing and a computer readable form of the Sequence Listing are provided herewith in accordance with 37 C.F.R. §1.821-1.825. The Sequence Listing information recorded in computer readable form is believed to be identical to the written Sequence

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Listing. Submission of the Sequence Listing does not include new matter.

Applicants also submit herewith a copy of the Search Report from the European Patent Office, together with copies of the references cited therein, which are listed on the attached Form PTO-1449.

Respectfully submitted,

Ira J. Schultz
Registration No. 28,666

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DENNISON, SCHEINER, SCHULTZ & WAKEMAN
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
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MARKED UP COPY OF AMENDED CLAIMS

Claims 1-20 have been canceled.

--23. (Amended) The pharmaceutical composition according to claim 21 **[or 22]** wherein said peptide analogue has the formula (SEQ ID N° : 1) :

A1-A2-A3-A4-A5-A6-A7-A8-Pro-Z(A)

in which :

- A1 is pGlu ; D-pGlu ; Sar ; AcSar ; Pro or a derivative thereof ; Ser ; D-Ser ; Ac-D-Ser ; Thr ; D-Thr ; Ac-D-Thr ; or an aromatic D-amino acid which may be acylated ;
- A2 is a direct bond ; His ; or an aromatic D-amino acid;
- A3 is an aromatic L- or D-amino acid;
- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;
- A5 is an aromatic L-amino acid ; or a basic L- or D-amino acid;
- A6 is Gly ; (S)-spirolactam-Pro ; D-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t) ; D-Ser(OR_1) where R_1 is a sugar moiety ; an aza-amino acid ; D-His which may be substituted on the imidazole ring by a (C_1-C_6)alkyl, a (C_2-C_7)acyl or a benzyl group ; an aliphatic D-

amino acid with a (C_1-C_8)alkyl or a (C_3-C_6)cycloalkyl side chain ; an aromatic D-amino acid ; D-cyclohexadienyl-Gly ; D-perhydronaphthyl-Ala ; D-perhydrodiphenyl-Ala ; or a basic L- or D-amino acid;

- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C_1-C_4)alkyl group optionally substituted by one or several fluorine atoms;

- A8 is a basic L- or D-amino acid ;

- Z is $GlyNH_2$; $D\text{-}AlaNH_2$; $azaGlyNH_2$; or a group $-NHR_2$ where R_2 is a (C_1-C_4)alkyl which may be substituted by an hydroxy or one or several fluorine atoms ; a (C_3-C_6)cycloalkyl ; or a heterocyclic radical selected from morpholinyl, pyrrolidinyl and piperidyl.

28. (Amended) The pharmaceutical composition according to **[one of claims 24 to 27]** **claim 24** wherein the peptide analogue is selected from the group consisting of leuprorelin, $[Npg^7]$-leuprorelin, triptorelin, $[Npg^7]$-triptorelin, goserelin, $[Npg^7]$-goserelin, buserelin and $[Npg^7]$-buserelin.

31. (Amended) The pharmaceutical composition according to claim 29 **[or 30]** wherein the peptide analogue is selected from

the group consisting of antide, [Npg^7]-antide, cetrorelix, [Npg^7]-cetrorelix, abarelix and [Npg^7]-abarelix.

32. (Amended) The pharmaceutical composition according to **[one of claims 21 to 31]** **claim 21** wherein the α-cyclodextrin derivative is selected from the group consisting of methylated α-cyclodextrin, hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin, carboxy-methylated α-cyclodextrin and phosphated α-cyclodextrin.

33. (Amended) The pharmaceutical composition according to **[claims 21 to 32]** claim 21 wherein the α-cyclodextrin derivative is hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin in combination with the LH-RH peptide analogue.

34. (Amended) The pharmaceutical composition according to **[one of claims 21 to 33]** **claim 21** which further comprises **a compound selected from the group consisting of** a protease inhibitor **[and/or]**, an absorption enhancer**, and mixtures thereof**.

41. (Amended) The method according to **[one of claims 37 to 40]** **claim 37** wherein the peptide analogue is selected from the group consisting of leuprorelin, [Npg^7]-leuprorelin,

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612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
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703 412-1155

triptorelin, [Npg^7]-triptorelin, goserelin, [Npg^7]-goserelin, buserelin and [Npg^7]-buserelin.

44. (Amended) The method according to claim 42 **[or 43]** wherein the peptide analogue is selected from the group consisting of antide, [Npg^7]-antide, cetrorelix, [Npg^7]-cetrorelix, abarelix and [Npg^7]-abarelix.

45. (Amended) The method according to **[one of claims 35 to 44] <u>claim 35</u>** wherein the α-cyclodextrin derivative is selected from the group consisting of methylated α-cyclodextrin, hexakis(2,3,6-tri-O-methyl)- α-cyclodextrin, carboxymethylated α-cyclodextrin and phosphated α-cyclodextrin.

52. (Amended) The method according to **[one of claims 48 to 51] <u>claim 48</u>** wherein the peptide analogue is selected from the group consisting of leuprorelin, [Npg^7]-leuprorelin, triptorelin, [Npg^7]-triptorelin, goserelin, [Npg^7]-goserelin, buserelin and [Npg^7]-buserelin.

55. (Amended) The method according to claim 53 **[or 54]** wherein the peptide analogue is selected from the group consisting of antide, [Npg^7]-antide, cetrorelix, [Npg^7]-cetrorelix, abarelix and [Npg^7]-abarelix.

56. (Amended) The method according to **[one of claims 47 to 55]** **claim 47** wherein the α-cyclodextrin derivative is selected from the group consisting of methylated α-cyclodextrin, hexakis(2,3,6-tri-O-methyl)- α-cyclodextrin, carboxymethylated α-cyclodextrin and phosphated α-cyclodextrin.

58. (Amended) The method according to **[one of claims 47 to 57]** **claim 47** for the treatment or prevention of breast cancer.

60. (Amended) The method according to **[one of claims 47 to 57]** **claim 47** for the treatment or prevention of prostate cancer or benign prostatic hypertrophy.

62. (Amended) The method according to **[one of claims 47 to 61]** **claim 47** wherein the peptide analogue is delivered to the gastrointestinal tract of the patient.

Claims 63-78 were added.

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Pharmaceutical compositions based on alpha-cyclodextrin for the oral administration of LH-RH analogues

The present invention relates to the pharmaceutical field. More specifically, the invention relates to the use of α-cyclodextrin or derivatives thereof for the preparation of pharmaceutical compositions for the oral administration of LH-RH (luteinizing hormone - releasing hormone) peptide analogues. The invention also relates to oral pharmaceutical compositions containing LH-RH peptide analogues in combination with α-cyclodextrin.

Natural and modified cyclodextrins (CDs) are well known ingredients used in a large variety of pharmaceutical preparations taking advantage of one or several of their properties relating to drug solubilization and stabilization (Loftsson and Brewster, 1996, *J. Pharm. Sci.*, **85**(10): 1017-1025) or to overall improvement of *in vivo* drug delivery (Rajewski and Stella, 1996, *J. Pharm. Sci.*, **85**(11): 1142-1169). CDs are cyclic oligosaccharides containing at least 6 α-D-(+)-glucopyranose units attached by α(1-4) glucoside bonds (Nash, *Handbook of Pharmaceutical Excipients*, ed. by Wade and Weller, 1994, American Pharmaceutical Association, Washington, and The Pharmaceutical Press, London, pp 145-148); the three most common CDs are α-, β- and γ-CD which consist of 6, 7 and 8 sugar units, respectively. Numerous derivatives of each type of CD can be obtained by random or controlled modifications of one, several or all free hydroxyl groups of the sugar moities.

LH-RH is a neurohormone produced by hypothalamic neurons and secreted in the pituitary portal vasculature to stimulate the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) by the pituitary gland. In turn, LH and FSH regulate the endocrine and germinal functions of the ovary in the female and of the testis in the male. LH-RH is a peptide of the following structure: pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2. Numerous normal or reduced-size, linear or cyclic peptide analogues of LH-RH incorporating natural, unusual or chemically-modified amino-acids have been synthesized over the years to yield potent agonist or antagonistic properties (Karten and Rivier, 1986, *Endocr. Rev.*, **7**(1): 44-66; Dutta, 1988, *Drugs of the Future*, **13**(8): 761-787; Kutscher et al., 1997, *Angew. Chem. Int. Ed. Engl.*, **36**: 2148-2161). Due to their total or partial peptide structure, however, all these analogues show poor oral bioavailability and bioactivity.

To date, only non-oral administration of LH-RH peptide analogues, has been reported. For example, Matsubara et al. (1996, J. Pharm. Sci., **84**(11) : 1295-1300) describe a nasal formulation of buserelin, based on dimethyl-β-CD, with improved bioavailability.

There is therefore a need, for the patients' comfort, to provide formulations which enable the oral administration of LH-RH peptide analogues.

It has now surprisingly been found that α-CD or its derivatives, enhance the biological activity of LH-RH peptide analogues when orally administered.

Thus, according to one of its feature, the invention relates to the use of α-cyclodextrin or derivatives thereof for the preparation of pharmaceutical compositions for the oral administration of LH-RH peptide analogues.

Examples of LH-RH peptide analogues which can be used within the scope of the invention include those described in International patent applications WO 98/21229 and WO 98/55505, the content of which is incorporated by reference, as well as standard agonists and antagonists of LH-RH, such as for example buserelin, nafarelin, leuprorelin, goserelin, histrelin, triptorelin, deslorelin, lutrelin, avorelin, cetrorelix, antide, ganirelix, azaline B, antarelix, detirelix, ramorelix, teverelix or abarelix.

Preferably, these peptide analogues have the formula (SEQ ID N° : 1) :

A1-A2-A3-A4-A5-A6-A7-A8-Pro-Z (A)

in which :

- A1 is pGlu ; D-pGlu ; Sar ; AcSar ; Pro or a derivative thereof such as AcPro, ForPro, OH-Pro, Ac-OH-Pro, dehydro-Pro or Ac-dehydro-Pro ; Ser ; D-Ser ; Ac-D-Ser ; Thr ; D-Thr ; Ac-D-Thr ; or an aromatic D-amino acid which may be acylated, such as D-Phe, D-HPhe, D-Tyr, D-HTyr, D-Trp, D-2MeTrp, D-Nal, D-1Nal, D-diphenyl-Ala, D-Bal, D-Pal, D-4Pal or D-Qal, where D-Phe, D-HPhe, D-Tyr, D-HTyr, and D-Trp may be substituted by one or more halogens, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, nitro or trifluoromethyl groups;

- A2 is a direct bond ; His ; or an aromatic D-amino acid such as D-Phe, D-HPhe, D-Tyr, D-HTyr, D-Trp, D-2MeTrp, D-Nal, D-1Nal, D-diphenyl-Ala, D-Bal, D-Pal, D-4Pal or D-Qal, where D-Phe, D-HPhe, D-Tyr, D-HTyr and D-Trp may be substituted by one or more halogens, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, nitro or trifluoromethyl groups;

- A3 is an aromatic L- or D-amino acid such as Phe, HPhe, Tyr, HTyr, Trp, 2MeTrp, Nal, 1Nal, diphenyl-Ala, Bal, Pal, 4Pal or Qal, where Phe, HPhe, Tyr, HTyr and Trp may be substituted by one or more halogens, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, nitro or trifluoromethyl groups;

- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;

- A5 is an aromatic L-amino acid such as Phe, HPhe, Tyr, HTyr, Trp, 2MeTrp, Nal, 1Nal, diphenyl-Ala, Bal, Pal, 4Pal or Qal, where Phe, HPhe, Tyr, HTyr and Trp may be substituted by one or more halogens, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, nitro or trifluoromethyl groups and/or N-alpha-substituted by a $(C_1\text{-}C_4)$alkyl group optionally substituted by one or several fluorine atoms ; or a basic L- or D-amino acid such as Arg, HArg, Orn, Lys, HLys, Cit, HCit, APhe or ACha, where Arg and HArg may be N-substituted by a $(C_1\text{-}C_6)$alkyl or a $(C_3\text{-}C_6)$cycloalkyl group on one or both nitrogen atoms, and where Orn, Lys, HLys, APhe and ACha may be N-substituted by one or two $(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_6)$cycloalkyl groups, or by an aminotriazolyl or a nicotinoyl, isonicotinoyl, 6-methyl-nicotinoyl, glycyl-nicotinoyl, nicotinyl-azaglycyl, furyl, glycyl-furyl, furyl-azaglycyl, pyrazinyl, pyrazinyl-carbonyl, picolinoyl, 6-methyl-picolinoyl, shikimyl, shikimyl-glycyl, Fmoc or Boc group;

- A6 is Gly ; (S)-spirolactam-Pro ; D-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Asn ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t) ; D-Ser(OR_1) where R_1 is a sugar moiety ; an aza-amino acid such as azaGly or azaAla ; D-His which may be substituted on the imidazole ring by a $(C_1\text{-}C_6)$alkyl, a $(C_2\text{-}C_7)$acyl or a benzyl group ; an aliphatic D-amino acid with a $(C_1\text{-}C_8)$alkyl or a $(C_3\text{-}C_6)$cycloalkyl side chain such as D-Ala, D-Abu, D-Aib, D-3Aib, D-Val, D-Nva, D-Leu, D-Ile, D-Tle, D-Nle, D-Hol, D-Npg, D-CPa, D-Cpa, D-Cba or D-Cha ; an aromatic D-amino acid such as D-Phe, D-HPhe, D-Tyr, D-HTyr, D-Trp, D-2MeTrp, D-Nal, D-1Nal, D-diphenyl-Ala, D-anthryl-Ala, D-phenanthryl-Ala, D-benzhydryl-Ala, D-fluorenyl-Ala, D-Bal, D-Pal, D-4Pal or D-Qal, where D-Phe, D-HPhe, D-Tyr, D-HTyr and D-Trp may be substituted by one or more halogens, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, nitro or trifluoromethyl groups ; D-cyclohexadienyl-Gly ; D-perhydronaphthyl-Ala ; D-perhydrodiphenyl-Ala ; or a basic L- or D-amino acid such as Arg, HArg, Orn, Lys, HLys, Cit, HCit, APhe or ACha, where Arg and HArg may be N-substituted by a $(C_1\text{-}C_6)$alkyl or a $(C_3\text{-}C_6)$cycloalkyl group on one or both nitrogen atoms, and where Orn, Lys, HLys, APhe and ACha may be N-substituted by one or two $(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_6)$cycloalkyl groups, or by an aminotriazolyl or a nicotinoyl, isonicotinoyl, 6-methyl-nicotinoyl, glycyl-nicotinoyl, nicotinyl-azaglycyl, furyl, glycyl-furyl, furyl-azaglycyl, pyrazinyl, pyrazinyl-carbonyl, picolinoyl, 6-methyl-picolinoyl, shikimyl, shikimyl-glycyl, Fmoc or Boc group;

- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms such as Ala, Abu, Aib, 3Aib, Val, Nva, Leu, Ile, Tle, Nle, Hol, Npg, CPa, Cpa,

Cba, Cha or Ada, which may be N-alpha-substituted by a (C_1-C_4)alkyl group optionally substituted by one or several fluorine atoms ;

- A8 is a basic L- or D-amino acid such as Arg, HArg, Orn, Lys, HLys, Cit, HCit, APhe or ACha, where Arg or HArg may be N-substituted by a (C_1-C_6)alkyl or a (C_3-C_6)cycloalkyl group on one or both nitrogen atoms, and where Orn, Lys, HLys, APhe or ACha may be N-substituted by one or two (C_1-C_6)alkyl or (C_3-C_6)cycloalkyl groups, or by an aminotriazolyl or a nicotinoyl, isonicotinoyl, 6-methyl-nicotinoyl, glycyl-nicotinoyl, nicotinyl-azaglycyl, furyl, glycyl-furyl, furyl-azaglycyl, pyrazinyl, pyrazinyl-carbonyl, picolinoyl, 6-methyl-picolinoyl, shikimyl, shikimyl-glycyl, Fmoc or Boc group;

- Z is $GlyNH_2$; $D\text{-}AlaNH_2$; $azaGlyNH_2$; or a group $-NHR_2$ where R_2 is a (C_1-C_4)alkyl which may be substituted by an hydroxy or one or several fluorine atoms ; a (C_3-C_6)cycloalkyl ; or a heterocyclic radical selected from morpholinyl, pyrrolidinyl and piperidyl;

as well as their pharmaceutically acceptable salts.

In the present description the term "(C_1-C_4)alkyl" denotes methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl and t-butyl groups.

The term "(C_1-C_6)alkyl" denotes methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, s-pentyl, t-pentyl and hexyl groups.

The term "(C_1-C_8)alkyl" denotes methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, s-pentyl, t-pentyl, hexyl, heptyl and octyl groups ;

The term "(C_1-C_4)alkoxy" denotes a group -OR where R is a (C_1-C_4)alkyl.

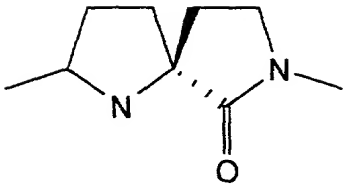
The term "(C_2-C_7)acyl" denotes a group -COR where R is a (C_1-C_6)alkyl.

The term "(C_3-C_6)cycloalkyl" denotes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups.

The term "sugar moiety" denotes D- or L-pentoses or hexoses and their amino-derivatives.

The term "LH-RH analogues" denotes peptides in which at least one amino acid has been modified in the sequence of LH-RH.

The term "(S)spirolactam-Pro" denotes the residue of the formula :



The term "oral administration" denotes the delivery of the peptide analogues of the invention to the gastrointestinal tract by means of an oral formulation or composition.

Peptidomimetic analogues of LH-RH defined by the absence of at least one peptide amide bond, as exemplified in the latest review by Kutscher et al. (1997, *Angew. Chem. Int. Ed. Engl.*, **36**: 2148-2161), are not considered within the scope of the present invention.

In the present description and in the claims, the following abbreviations are used :

Abu : 2-aminobutyric acid
Ac : acetyl
ACha : aminocyclohexylalanine
Aib : 2-aminoisobutyric acid
3Aib : 3-aminoisobutyric acid
Ala : alanine
$AlaNH_2$: alaninamide
APhe : p-aminophenylalanine
Arg : arginine
Asp : aspartic acid
azaAla : aza-alanine
azaGly : aza-glycine
$azaGlyNH_2$: azaglycinamide
Bal : benzothienylalanine
Boc : *tert*-butoxycarbonyl
Cba : cyclobutylalanine
Cha : cyclohexylalanine
Cit : citrulline
CPa : cyclopropylalanine
Cpa : cylopentylalanine
Fmoc : fluorenylmethoxycarbonyl
For : formyl
Glu : glutamic acid
Gly : glycine
$GlyNH_2$: glycinamide
HArg : homoarginine
HCit : homocitrulline
His : histidine
HLys : homolysine
Hol : homoleucine
Ile : isoleucine
IprLys : N^{ε}-isopropyllysine
Leu : leucine
Lys : lysine
MeSer : N-methylserine
Met : methionine
Nal : 3-(2-naphtyl)alanine
1Nal : 3-(1-naphtyl)alanine
NEt : N-ethylamide
NicLys : N^{ε}-nicotinoyllysine

Nle : norleucine
Nva : norvaline
OBzl : benzyl ester
Pal : 3-(3-pyridyl)alanine
Pen : penicillamine
Phe : phenylalanine
Qal : 3-(3-quinolyl)alanine
Ser : serine
(S-Et)Pen : S-ethyl-penicillamine
Tle : tert-leucine
Tyr : tyrosine
Ada : adamantylalanine
MeNpg : N-methylneopentylglycine
HTyr : homotyrosine
Bzl : benzyl
Asn : asparagine
MeTyr : N-methyltyrosine
Npg : neopentylglycine
OBu^t : *tert*-butoxy
Orn : ornithine
pClPhe : 3-(4-chlorophenyl)alanine
pGlu : pyroglutamic acid
Pro : proline
Sar : sarcosine
(S-Me)Pen : S-methyl-penicillamine
Thr : threonine
Trp : tryptophan
Val : valine
HPhe : homophenylalanine
4Pal : 3-(4-pyridyl)alanine
2MeTrp : 2-methyltryptophan
SPL : (S)spirolactam-Pro
MeLeu : N-methylleucine
MeHTyr : N-methylhomotyrosine

A preferred group of peptide analogues (A) comprises the peptides of the formula (SEQ ID N° : 2) :

A1-His-A3-A4-A5-A6-A7-A8-Pro-Z (I)

in which:

- A1 is pGlu, Sar or AcSar;

- A3 is an aromatic L-amino acid such as Phe, HPhe, Tyr, HTyr, Trp, 2MeTrp, Nal, 1Nal, diphenyl-Ala, Bal, Pal, 4Pal or Qal, where Phe, HPhe, Tyr, HTyr and Trp may be substituted by one or more halogens, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, nitro or trifluoromethyl groups;

- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;

- A5 is an aromatic L-amino acid such as Phe, HPhe, Tyr, HTyr, Trp, 2MeTrp, Nal, 1Nal, diphenyl-Ala, Bal, Pal, 4Pal or Qal, where Phe, HPhe, Tyr, HTyr and Trp may be substituted by one or more halogens, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, nitro or trifluoromethyl groups;

- A6 is Gly ; D-Pro ; (S)-spirolactam-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t) ; D-Ser(OR$_1$) where R$_1$ is a sugar moiety ; an aza-amino acid such as azaGly or azaAla ; D-His which may be substituted on the imidazole ring by a (C$_1$-C$_6$)alkyl or a benzyl group ; an aliphatic D-amino acid with a (C$_1$-C$_8$)alkyl or a (C$_3$-C$_6$)cycloalkyl side chain such as D-Ala, D-Abu, D-Aib, D-3Aib, D-Val, D-Nva, D-Leu, D-Ile, D-Tle, D-Nle, D-Hol, D-Npg, D-CPa, D-Cpa, D-Cba or D-Cha ; an aromatic D-amino acid such as D-Phe, D-HPhe, D-Tyr, D-HTyr, D-Trp, D-2MeTrp, D-Nal, D-1Nal, D-diphenyl-Ala, D-anthryl-Ala, D-phenanthryl-Ala, D-benzhydryl-Ala, D-fluorenyl-Ala, D-Bal, D-Pal, D-4Pal or D-Qal, where D-Phe, DHPhe, D-Tyr, D-HTyr and D-Trp may be substituted by one or more halogens, (C$_1$-C$_4$)alkyl, (C$_1$-C$_4$)alkoxy, nitro or trifluoromethyl groups ; D-cyclohexadienyl-Gly ; D-perhydronaphtyl-Ala ; D-perhydrodiphenyl-Ala ; or a basic D-amino acid such as D-Arg, D-HArg, D-Orn, D-Lys, D-HLys, D-Cit, D-HCit, D-APhe optionally substituted by an aminotriazolyl group or D-ACha, where D-Arg and D-HArg may be be N-substituted by a (C$_1$-C$_6$)alkyl or (C$_3$-C$_6$)cycloalkyl groups, or by a Fmoc or Boc group;

- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms such as Ala, Abu, Aib, 3Aib, Val, Nva, Leu, Ile, Tle, Nle, Hol, Npg, CPa, Cpa, Cba, Cha or Ada, which may be N-alpha-substituted by a (C$_1$-C$_4$)alkyl group optionally substituted by one or several fluorine atoms;

- A8 is a basic L-amino acid such as Arg, HArg, Orn, Lys, HLys, Cit, HCit, APhe optionally substituted by an aminotriazolyl group, or ACha;

- Z is GlyNH$_2$; azaGlyNH$_2$; or a group -NHR$_2$ where R$_2$ is a (C$_1$-C$_4$)alkyl which may be substituted by an hydroxy or one or several fluorine atoms ; a (C$_3$-C$_6$)cycloalkyl ; or a heterocyclic radical selected from morpholinyl, pyrrolidinyl and piperidyl;

as well as their pharmaceutically acceptable salts.

Among the peptide analogues of formula (I), those of the formula (SEQ ID N° : 3) :

pGlu-His-A3-Ser-A5-A6-A7-Arg-Pro-Z (II)

in which:

- A3 and A5 are aromatic L-amino acids as defined for (I) ;

- A6 is as defined for (I) ;

- A7 is Leu, Tle, Nle, Hol, Npg, Cha or Ada, which may be N-alpha-substituted by a methyl or ethyl group optionally substituted by one or several fluorine atoms;

- Z is as defined for (I) ;

as well as their pharmaceutically acceptable salts,

are preferred.

Especially preferred are the peptide analogues of the formula (SEQ ID N° : 4) :

pGlu-His-A3-Ser-A5-A6-A7-Arg-Pro-Z (III)

in which:

- A3 and A5 are each independently Phe, Tyr, Trp, 2MeTrp, HPhe, HTyr, Nal, 1Nal, Bal, Pal, 4Pal, or pClPhe ;

- A6 is (S)-spirolactam-Pro ; Gly; D-Pro ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t); D-His or D-His(Bzl) ; D-Ala, D-Leu, D-Tle, D-Nle, D-Hol, D-Npg or D-Cha ; D-Phe, D-HPhe, D-Tyr, D-HTyr, D-Trp, D-2MeTrp, D-Nal, D-1Nal, D-Bal, D-Pal, D-4Pal, or D-pClPhe; D-cyclohexadienyl-Gly ; D-perhydronaphtyl-Ala ; D-perhydrodiphenyl-Ala ; or D-APhe optionally substituted by an aminotriazolyl group ;

- A7 is Leu, Npg or Cha, which may be N-alpha-substituted by a methyl group;

- Z is $GlyNH_2$; $azaGlyNH_2$ or $-NC_2H_5$.

Also especially preferred are the peptide analogues of the formula (SEQ ID N° : 5) :

pGlu-His-Trp-Ser-Tyr-A6-A7-Arg-Pro-Z (IV)

in which:

- A6 is (S)-spirolactam-Pro, D-Leu, D-Ala, D-Nal, D-Phe, D-Ser(OBu^t) or D-Trp;

- A7 is Leu, MeLeu, Npg or MeNpg;

- Z is $GlyNH_2$; $azaGlyNH_2$ or $-NC_2H_5$.

The peptide analogues of formula (I) to (IV) in which A7 is Npg are especially preferred.

Representative peptide analogues of formula (I) to (IV) include leuprorelin, [Npg^7]-leuprorelin, triptorelin, [Npg^7]-triptorelin, goserelin, [Npg^7]-goserelin, buserelin and [Npg^7]-buserelin.

Another preferred group of peptide analogues (A) comprises the peptides of the formula (SEQ ID N° : 6) :

A1-A2-A3-A4-A5-A6-A7-A8-Pro-Z (I')

in which:

- A1 is pGlu ; D-pGlu ; Sar ; AcSar ; Pro or a derivative thereof such as AcPro, ForPro, OH-Pro, Ac-OH-Pro, dehydro-Pro or Ac-dehydro-Pro ; Ser ; D-Ser ; Ac-D-Ser ; Thr ; D-Thr ; Ac-D-Thr ; or an aromatic D-amino acid which may be acylated, preferably acetylated, such as D-Phe, D-HPhe, D-Tyr, D-Trp, D-Nal, D-1Nal, D-diphenyl-Ala, D-Bal, D-Pal, D-4Pal or D-Qal, where D-Phe and D-Trp may be substituted by one or more halogens, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, nitro or trifluoromethyl groups;

- A2 is a direct bond or an aromatic D-amino acid such as D-Phe, D-HPhe, D-Tyr, D-Trp, D-Nal, D-1Nal, D-diphenyl-Ala, D-Bal, D-Pal, D-4Pal or D-Qal, where D-Phe and D-Trp may be substituted by one or more halogens, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, nitro or trifluoromethyl groups;

- A3 is an aromatic L- or D-amino acid such as Phe, HPhe, Tyr, Trp, Nal, 1Nal, diphenyl-Ala, Bal, Pal, 4Pal or Qal, where Phe and Trp may be substituted by one or more halogens, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, nitro or trifluoromethyl groups;

- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;

- A5 is an aromatic L-amino acid such as Phe, HPhe, Tyr, HTyr, Trp, Nal, 1Nal, diphenyl-Ala, Bal, Pal, 4Pal or Qal, where Phe, Tyr, HTyr and Trp may be substituted by one or more halogens, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, nitro or trifluoromethyl groups and/or N-alpha-substituted by a (C_1-C_4)alkyl group optionally substituted by one or several fluorine atoms; or a basic L- or D-amino acid such as Arg, HArg, Orn, Lys, HLys, Cit, HCit, APhe or ACha, where Arg and HArg may be N-substituted by a (C_1-C_6)alkyl or (C_3-C_6)cycloalkyl group on one or both nitrogen atoms, and where Orn, Lys, HLys, APhe and ACha may be N-substituted by one or two (C_1-C_6)alkyl or (C_3-C_6)cycloalkyl groups, or by a nicotinoyl, isonicotinoyl, 6-methyl-nicotinoyl, glycyl-nicotinoyl, nicotinyl-azaglycyl, furyl, glycyl-furyl, furyl-azaglycyl, pyrazinyl, pyrazinyl-carbonyl, picolinoyl, 6-methyl-picolinoyl, shikimyl, shikimyl-glycyl, Fmoc or Boc group;

- A6 is Gly ; (S)-spirolactam-Pro ; D-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Asn ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(O-Bu^t) ; D-Thr(O-Bu^t) ; D-Cys(O-Bu^t) ; D-Ser(O-R_1) where R_1 is a sugar moiety ; an aliphatic D-amino acid with a (C_1-C_8)alkyl or a (C_3-C_6)cycloalkyl side chain such as D-Ala, D-Abu, D-Aib, D-3Aib, D-Val, D-Nva, D-Leu, D-Ile, D-Tle, D-Nle, D-Hol, D-

Npg, D-CPa, D-Cpa, D-Cba or D-Cha ; an aromatic D-amino acid such as D-Phe, D-HPhe, D-Tyr, D-Trp, D-Nal, D-1Nal, D-diphenyl-Ala, D-anthryl-Ala, D-phenanthryl-Ala, D-benzhydryl-Ala, D-fluorenyl-Ala, D-Bal, D-Pal, D-4Pal or D-Qal, where D-Phe and D-Trp may be substituted by one or more halogens, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, nitro or trifluoromethyl groups ; D-cyclohexadienyl-Gly ; D-perhydronaphthyl-Ala ; D-perhydrodiphenyl-Ala ; or a basic L- or D-amino acid such as Arg, HArg, Orn, Lys, HLys, Cit, HCit, APhe or ACha, where Arg and HArg may be N-substituted by a (C_1-C_6)alkyl or (C_3-C_6)cycloalkyl group on one or both nitrogen atoms, and where Orn, Lys, HLys, APhe and ACha may be N-substituted by one or two (C_1-C_6)alkyl or (C_3-C_6)cycloalkyl groups, or by a nicotinoyl, isonicotinoyl, 6-methyl-nicotinoyl, glycyl-nicotinoyl, nicotinyl-azaglycyl, furyl, glycyl-furyl, furyl-azaglycyl, pyrazinyl, pyrazinyl-carbonyl, picolinoyl, 6-methyl-picolinoyl, shikimyl, shikimyl-glycyl, Fmoc or Boc group;

- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms such as Ala, Abu, Aib, 3Aib, Val, Nva, Leu, Ile, Tle, Nle, Hol, Npg, CPa, Cpa, Cba, Cha or Ada, which may be N-alpha-substituted by a (C_1-C_4)alkyl group optionally substituted by one or several fluorine atoms ;

- A8 is a basic L- or D-amino acid such as Arg, HArg, Orn, Lys, HLys, Cit, HCit, APhe or ACha, where Arg and HArg may be N-substituted by a (C_1-C_6)alkyl or (C_3-C_6)cycloalkyl group on one or both nitrogen atoms, and where Orn, Lys, HLys, APhe and ACha may be N-substituted by one or two (C_1-C_6)alkyl or (C_3-C_6)cycloalkyl groups, or by a nicotinoyl, isonicotinoyl, 6-methyl-nicotinoyl, glycyl-nicotinoyl, nicotinyl-azaglycyl, furyl, glycyl-furyl, furyl-azaglycyl, pyrazinyl, pyrazinyl-carbonyl, picolinoyl, 6-methyl-picolinoyl, shikimyl, shikimyl-glycyl, Fmoc or Boc group;

- Z is $GlyNH_2$ or $D\text{-}AlaNH_2$;

as well as their pharmaceutically acceptable salts.

Among the peptides of formula (I'), those of the formula (SEQ ID N° : 7):

Ac-D-Nal-D-pClPhe-D-Pal-Ser-A5-A6-A7-A8-Pro-$D\text{-}AlaNH_2$ (II')

in which :

- A5 is Tyr, HTyr, MeTyr, MeHTyr, NicLys or IprLys;

- A6 is (S)-spirolactam-Pro, D-Arg, D-NicLys, D-IprLys, D-Cit, D-HCit or D-Asn;

- A7 is Leu, MeLeu, Npg or MeNpg;

- A8 is Arg, NicLys or IprLys;

and their pharmaceutically acceptable salts,

are preferred.

The peptide analogues of formula (I') and (II') in which A7 is Npg are especially preferred.

Representative peptide analogues of formula (I') and (II') include antide, [Npg^7]-antide, cetrorelix, [Npg^7]-cetrorelix, abarelix and [Npg^7]-abarelix.

Further preferred peptide analogues comprise those of formula (A) where A6 is as defined therein except D-Asn.

Examples of the salts with pharmaceutically acceptable acids are those with mineral acids, such as for example the hydrochloride, hydrobromide, sulfate, phosphate, borate, hydrogensulfate, dihydrogenphosphate or nitrate, and those with organic acids, such as for example the acetate, oxalate, tartrate, succinate, maleate, fumarate, gluconate, citrate, pamoate, malate, ascorbate, benzoate, p-toluenesulfonate or naphtalenesulfonate.

Examples of the salts with pharmaceutically acceptable bases are those with alkali or alkaline earth metals such as sodium, potassium, calcium or magnesium, and those with organic bases such as amines, trometamol, N-methylglutamine, and the like.

The peptides used in the present invention can be prepared by the well-known techniques of peptide chemistry such as for example peptide synthesis in solution or solid phase peptide synthesis. In general, these techniques involve the stepwise addition of one or more amino acids -which may be suitably protected- to a forming peptide chain. Reference can for example be made to *Synthetic Peptides: a user's guide*, ed. by G.A. Grant, 1992, UWBC Biotechnical Resource Series, Washington University Press, Saint-Louis, USA.

Each molecule of α-CD bears 6 primary hydroxyl groups and 12 secondary hydroxyl groups, respectively correspondind to the 6-OH and to the 2- and 3-OH groups of each of the 6 glucopyranose units. Another general aspect of the present invention concerns α-CD and its derivatives which are defined as the result of chemical or biochemical modifications involving a precise or average number between 1 and 18 hydroxyl groups of the α-CD molecule, in a random or regioselective fashion, with one or several different types of reactions such as oxidation, reduction, alkylation, hydroxyalkylation, esterification with organic or

mineral acids, intramolecular dehydration, tosylation followed by reductive amination or halogen substitution, sugar branching or further polymerization, and their different possible combinations and mixtures. Examples of α-CD derivatives include α-CD modified with one or more groups selected from methyl, carboxymethyl, ethyl, butyl, octyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, acetyl, propionyl, butyryl, succinyl, benzoyl, palmityl, sulfonyl, toluenesulfonyl, amino, aminopropyl, glucosyl, maltosyl, dimaltosyl, carboxymethyl ether, sulfobutylether, and phosphate ester.

Preferred α-CD derivatives according to the invention comprise methylated α-CD ; hexakis(2,3,6-tri-O-methyl)-α-CD, also known as "permethylated" α-CD ; carboxymethylated α-CD and phosphated α-CD. α-CD and hexakis(2,3,6-tri-O-methyl)-α-CD are especially advantageous when used in the preparation of the pharmaceutical compositions of the invention.

As mentioned above, α-CD or its derivatives enhance the biological activity of LH-RH peptide analogues in oral pharmaceutical compositions.

Thus, according to another feature, the invention relates to oral pharmaceutical compositions which comprise as the active principle a LH-RH peptide analogue as defined above in the form of a combination with α-CD or a derivative thereof, said compositions being intended to be delivered to the gastrointestinal tract.

The peptides according to the general formula (I) exert an agonist activity upon the LH-RH receptors *in vivo*, resulting in the stimulation of LH secretion by the pituitary, which, in males, stimulates the secretion of testosterone by the testis.

Adult male Sprague-Dawley rats were orally administered by gavage an oral formulation comprising leuprorelin (LEU, Bachem), triptorelin (TRI, Bachem), deslorelin (DES, Saxon Biochemicals), goserelin (GOS, Saxon Biochemicals) or the other following example analogues: example 1 ([(S)spirolactam(Pro^6, Npg^7), desGly^{10}-ProNEt^9]LH-RH), example 2 ([D-Ala^6, Npg^7, desGly^{10}-ProNEt^9]LH-RH), example 3 ([Npg^7]leuprorelin), example 4 ([D-Phe^6, Npg^7, desGly^{10}-ProNEt^9]LH-RH), example 5 ([Npg^7]triptorelin) and example 6 ([D-Ala^6, desGly^{10}-ProNet^9]LH-RH, Bachem), in combination with α-CD (Sigma or Wacker Chemie). As a comparison, the same agonists have been orally administered by gavage in a standard aqueous vehicle not comprising α-CD (comparative examples). For screening purposes, blood samples were drawn 2 hours after oral administration of a common dose of 2 nmoles/rat of LH-RH peptide agonists in an aqueous solution containing 10 or 100

mM of α-CD (Tables 1 and 2; Figures 1, 4 and 6). For kinetic purposes, the effects of 2 nmoles/rat of example 3 with or without 100 mM of α-CD were tested between 0.5 and 8 hours on plasma LH and testosterone levels (Figures 2 and 5). The influence of increasing concentrations of α-CD (5%, 10% or 14%) was tested with example 2 at the dose of 5 μg/kg 2 hours after oral administration (Figure 3). Total plasma testosterone (Diagnostic System Laboratories) and LH (Amersham Pharmacia Biotech) determinations were performed by radioimmunoassay. In screening 2-hour experiments, each group comprised between 6 and 8 rats; each time point of the kinetic study was studied on four animals.

Table 1 : stimulation of testosterone secretion

Compound without α-CD	total plasma testosterone (nmol/l) (m ± sem)	Compound with α-CD	total plasma testosterone (nmol/l) (m ± sem)
Control	8.6 ± 3.32	Control (α-CD)	3.8 ± 0.66
Triptorelin	25.8 ± 3.14	Triptorelin (α-CD)	61.9 ± 6.01
Leuprorelin	26.3 ± 5.77	Leuprorelin (α-CD)	70.7 ± 4.06
Goserelin	21.4 ± 5.99	Goserelin (α-CD)	66.5 ± 6.19
Deslorelin	9.7 ± 2.41	Deslorelin (α-CD)	48.2 ± 7.29
C. ex 1	40.1 ± 6.78	Example 1	58.0 ± 8.75
C. ex 2	23.0 ± 8.54	Example 2	72.8 ± 4.64
C. ex 3	39.7 ± 8.11	Example 3	69.7 ± 3.6
C. ex 4	30.1 ± 5.86	Example 4	67.9 ± 9.11
C. ex 5	15.8 ± 4.24	Example 5	52.1 ± 6.99
C. ex 6	28.3 ± 4.56	Example 6	61.8 ± 5.10

As can be seen from the above results as well as from Figures 1-4, oral formulations with α-CD significantly enhance the stimulation of testosterone secretion induced by LH-RH analogues. Especially, deslorelin alone was inactive at this threshold dose of 2 nmoles/rat, but showed a marked potency when formulated with α-CD. The crucial role played by α-CD is demonstrated by the concentration-dependance of its effect : combined with 10 mM α-CD (0.972%), the oral activity of example 3 was not significantly improved (Figure 1) ; at 5% (51.4 mM), α-CD did

enhance the stimulation of testosterone secretion induced by example 2 by oral administration, although not to the maximal level achieved with 10% (103 mM) as well as 14% (144 mM) (Figure 3).

It is also worth noting (see figures 1 and 3) that β-CD, hydroxypropyl-β-CD (HP-β-CD) and γ-CD have no potentiating effect on the LH-RH analogue-induced stimulation of testosterone secretion.

Table 2 : stimulation of LH secretion

Compound without α-CD	total plasma LH (ng/ml) (m ± sem)	Compound with α-CD	total plasma LH (ng/ml) (m ± sem)
Control	1.2 ± 0.11	Control (α-CD)	1.1 ± 0.10
Triptorelin	1.4 ± 0.10	Triptorelin (α-CD)	10.1 ± 2.54
Leuprorelin	1.2 ± 0.14	Leuprorelin (α-CD)	12.3 ± 2.03
C. ex 1	1.5 ± 0.19	Example 1	7.1 ± 1.68
C. ex 2	1.6 ± 0.14	Example 2	19.7 ± 3.70
C. ex 3	2.2 ± 0.58	Example 3	10.9 ± 1.66
C. ex 4	1.4 ± 0.17	Example 4	16.1 ± 5.22
C. ex 5	1.4 ± 0.10	Example 5	3.2 ± 0.56

As can be seen from the above results as well as from Figures 5-6, the potentiating effect of α-CD in oral formulations containing LH-RH analogues on LH release is even more pronounced than on testosterone secretion : all tested LH-RH analogues were inactive when administered alone at the same dose of 2 nmoles/rat, whereas, depending on the analogue, they induced a 3- to 16-fold increase above control levels when administered in combination with α-CD.

Similar or even better results were obtained with α-CD derivatives such as methylated α-CD, hexakis(2,3,6-tri-O-methyl)-α-CD, carboxymethylated α-CD or phosphated α-CD. All α-CD derivatives were purchased from Cyclolab (Budapest, Hungary). The influence of α-CD derivatives were compared with that of α-CD itself on the potentiation of LH-RH agonist activity of example 3 when administered by gavage to rats at the low dose of 5 μg/kg p.o. : total testosterone plasma levels were measured 2 hours after administration (Table 3).

Table 3 : Stimulation of testosterone secretion by example 3

dose (μg/kg p.o.)	cyclodextrin (CD) type (concentration)	testosterone levels (ng/ml) ; (m ± sem)	n rats
0 (control)	none	1.0 ± 0.17	24
5	none	3.4 ± 0.79	16
5	carboxymethylated α-CD (50%)	6.9 ± 1.62	10
5	methylated α-CD (30%)	7.1 ± 1.59	10
5	phosphated α-CD (30%)	7.4 ± 2.00	10
5	α-CD (10%)	10.0 ± 1.22	24
5	permethylated α-CD (15%)	12.9 ± 1.10	10

The α-CD derivatives tested above at least doubled the effect of example 3 by oral administration. Native α-CD and its permethylated derivative appeared to be especially favorable with respectively a 2.9- and 3.8- fold enhancement of agonist activity of example 3 on testosterone at this dose level of 5 μg/kg p.o.

In a further experiment, example 3 was tested with α-CD or permethylated α-CD at an equal concentration of 10%. Two hours after administration, plasma LH levels were measured on eight rats per dose group (Figure 7). The 5 μg/kg p.o dose of example 3 alone was inactive on LH levels at this time point, and 10 and 20 μg/kg p.o. were clearly threshold doses in these experimental conditions.

Combination of example 3 with 10% α-CD resulted in slight but significant stimulations at 5 and 10 μg/kg p.o., and in a much greater effect at 20 μg/kg p.o. when compared with example 3 alone (over 5-fold enhancement of LH-releasing activity). Moreover, combination of example 3 with 10% permethylated α-CD resulted in an even higher potentiation : the doses of 2.5, 5 and 10 μg/kg p.o., which remained inactive when example 3 was given alone, yielded a sharp dose-related stimulatory response (Figure 7).

The peptides according to the general formula (I') exert an antagonist activity upon the LH-RH receptors *in vivo*, resulting in particular in the inhibition of ovulation.

The influence of α-, β- and γ-CD was tested on the activity of antide (an example of LH-RH peptide antagonist) when orally admininisted by gavage to normally cycling adult female Wistar rats between 1:30 and 3:00 p.m. on the day of proestrus, after at least two full regular estrous cycles as monitored by daily vaginal

smears. The antiovulatory efficacy was checked the next morning, on the day of expected estrus, by looking for ova in the oviduct of treated females. The presence of at least one ovum attested that some degree of spontaneous ovulation did occur, and only the total absence of ovum was considered as effective LH-RH antagonist-induced inhibition of ovulation. Antide was solubilized in a vehicle consisting of 20% (vol/vol) propylene glycol in water already containing 1% bovine albumin, to which 10% (wt/vol) of either α-, β- or γ-CD was then added. The results of the experiments are summarized in the following Table 4.

Table 4 : Inhibition of ovulation by oral administration of antide

oral formulation	antide (μg/rat p.o.)	n ovulations/ N treated rats	percentage of inhibition
vehicle only	0	24/24	0%
vehicle + α-CD (10%)	0	8/8	0%
vehicle only	200	8/8	0%
	400	19/22	14%
	600	5/8	44%
vehicle + α-CD (10%)	200	6/8	25%
	400	6/22	73%
	600	2/8	75%
vehicle + β-CD (10%)	400	7/7	0%
vehicle + γ-CD (10%)	400	7/7	0%

The vehicle with or without α-CD had no effect by itself. The threshold effective dose of antide by oral administration was 400 μg/kg p.o. with only 3 animals out of 22 showing inhibition of ovulation. Beta- and γ-CD had no influence on the minimal activity of antide at this dose level.

However, α-CD significantly enhanced antide potency from 14% to 73% of inhibition at 400 μg/kg. The twice lower dose of 200 μg/kg was even slightly effective (25% of inhibition) in combination with α-CD 10%. Therefore, α-CD was able to potentiate the activity of a LH-RH peptide antagonist by oral administration, but not β- or γ-CD.

The oral formulations of the invention can be prepared by methods well known to those skilled in the art, generally as follows : a known amount of a drug is added to an aqueous cyclodextrin solution in sufficient concentration; the drug-cyclodextrin interaction can take place in solution or suspension within minutes or after stirring for up to 1 week at the desired temperature with or without sonication, depending on the nature of the drug and of the cyclodextrin, and on their respective concentrations. Then, the resulting drug-cyclodextrin combination or complex can be further obtained in a dry form by filtration, centrifugation, evaporation or sublimation.

By way of illustration, the example combinations of LH-RH analogues with α-CD hereafter describe one basic method for the preparation of the formulations according to the invention in solution, notwithstanding their further processing to any appropriate dry form that will take advantage of the same potentiating properties.

Such formulations may further comprise, one or several other pharmaceutically appropriate excipients for oral administration such as lactose, fructose, glucose, sucrose, compressible sugar, saccharin, povidone, crospovidone, magnesium stearate, kaolin, bentonite, colloidal silica, mannitol, sorbitol, starch and its derivatives, microcrystalline or powdered cellulose, methylcellulose, carboxymethylcellulose, ethylcellulose or other chemically modified celluloses, other cyclodextrins, maltodextrin, dextrates, dextrin, dextrose, alginates, pectins, pectates, sorbitan esters, polysorbate 80, chitosan, guar or xanthan gums, mono-, di- or tri-ethanolamine, oleic acid or ethyl oleate, stearic acid, water, liquid glucose, propylene glycol, lactic acid, malic acid, ethanol, isopropyl myristate or palmitate, glycerin, glyceryl monooleate, glyceryl monostearate, glyceryl palmitostearate, lecithin, medium or short chain triglycerides, various oils from corn, cottonseed, olive, peanut, sesame or soybean, and the like. These formulations are administered by mouth (or naso-gastric tubing) in various aqueous or non-aqueous solutions or suspensions such as true solutions, syrups, elixirs, mucilages, jellies, gels, milks, magmas, macro-, micro-or nano-emulsions, or in various solid forms such as compressed, coated, buccal, sublingual, effervescent or molded tablets, hard or soft capsules, pills, troches or cachets. Enteric coatings of usual solid oral dosage forms or of soft capsules containing liquid formulations, and sustained, delayed or programmed gastric, enteric or colonic release forms or devices are preferred means to deliver the active principle.

The main target of LH-RH peptide agonists according to formula (I) is the pituitary gland, but direct actions have been reported on the gonads themselves (testis and ovary), on the thymus and some lymphoid cell lines, and on breast, prostate, pancreatic or nervous system tumors. They exert on any LH-RH sensitive target, either a stimulatory activity by short-term acute or pulsatile administration, or an inhibitory effect by repeated or continuous administrations that induce the desensitization and the down-regulation of LH-RH receptors. In the case of the hypothalamo-pituitary-gonadal axis, prolonged administration results in a so-called "chemical" castration.

The main target of LH-RH peptide antagonists according to formula (I') is also the pituitary gland, where they bind to the LH-RH receptors and prevent the activity of endogenous LH-RH. By this mechanism, the pituitary-gonadal axis can be inhibited. The programmed use of LH-RH antagonists can also be taken advantage of to obtain a spontaneous stimulation of the pituitary-gonadal axis at any given time by stopping their administration at an appropriate earlier time point.

Therefore, LH-RH agonists or antagonists according to formula (A) are useful in all situations where the actions of LH-RH must be either inhibited, prevented or stimulated. Especially, the peptide analogues of the invention are useful in the treatment of LH-RH-sensitive diseases, namely the diseases where a LH-RH agonist or antagonist action is required.

Accordingly, the oral pharmaceutical compositions of the invention can find an appropriate therapeutic use in humans as well as in animals, depending on doses and treatment regimens, in reproductive endocrinology and in the treatment or prevention of sex hormone-dependent benign or malignant tumors ; said treatment or prevention may involve parallel and/or sequential supplementary curative or preventive regimens based on other hormonal or antitumoral agents. LH-RH sensitive sex hormone-independent benign or malignant tumors can also regress upon treatment with the oral pharmaceutical compositions according to the invention, alone or associated with other parallel and/or sequential antitumoral treatments. Immune mechanisms can also be modified by the oral pharmaceutical compositions according to the invention, alone or associated with other parallel and/or sequential treatments based on immuno-modulating or -suppresive agents such as glucocorticoids, cyclosporin, rapamycin, tacrolimus, their derivatives, and the like. The oral pharmaceutical compositions according to the invention are

therefore very valuable in the treatment and prevention of autoimmune diseases, graft rejection or atopic diseases, and in the treatment of benign or malignant lymphoproliferative disorders.

The oral pharmaceutical compositions according to the invention are especially useful in the inhibition, planning and triggering of ovulation in *in vitro* fertilization programs, and in the treatment of male and female infertility or hypogonadic states. Conversely, they can also be used in male or female contraception or treatment of hypergonadic states. In both cases, said treatments may involve other parallel and/or sequential treatments with sex steroids and/or gonadotrophins. This applies to men and women, but also to wild or domestic animals in uses such as improvement or control of reproductive performance, or as a tool to optimize breeding strategies.

The oral pharmaceutical compositions according to the invention are also especially useful in men to treat advanced prostate cancer, but can also be used as a first line therapy in this indication and in benign prostatic hypertrophy ; in both cases, said treatments may also involve additional parallel and/or sequential treatments based on inhibitors of androgen action, i.e. antiandrogens such as cyproterone acetate, osaterone acetate, chlormadinone acetate, flutamide, nilutamide or bicalutamide and the like, and/or on 5α-reductase inhibitors such as finasteride, epristeride or turosteride and the like, and/or on C_{17-20} lyase inhibitors such as abiraterone and the like.

The oral pharmaceutical compositions according to the invention are also especially useful in the treatment or prevention of breast cancer in women and in men, especially estrogen receptor positive tumors ; said treatment or prevention may involve parallel or sequential supplementary curative or preventive regimens based on antiestrogens such as tamoxifen, raloxifen or droloxifen and the like, and/or on aromatase inhibitors such as atamestane, formestane, letrozole, anastrozole and the like, and/or on C_{17-20} lyase inhibitors such as abiraterone and the like. The oral pharmaceutical compositions according to the invention are also very useful in the treatment or prevention of certain estrogen receptor negative tumors that respond to the direct effects of LH-RH analogues or indirectly to their gonadal suppressive activity.

Other gynecological conditions, such as endometrial hyperplasia, leiomyoma, adenomyoma, endometriosis, polycystic ovary syndrome, hirsutism and benign

breast disease (pain, cysts or fibrosis), can also be prevented by or benefit from treatment with the oral pharmaceutical compositions according to the invention ; said treatment or prevention may involve additional parallel and/or sequential curative or preventive treatments based on antiestrogens (cited above), progestins such as cyproterone acetate, osaterone acetate, chlormadinone acetate, nomegestrol acetate, promegestone, demegestone, trimegestone and the like, and/or their contraceptive or post-menopausal replacement combination formulations with estrogens such as estradiol or ethynylestradiol. The oral compositions of the invention can also interfere with gestation by inducing abortion or by triggering labor ; in this case they may also be used in parallel or in sequence with treatments based on estrogens (cited above), antiprogestins such as mifepristone and/or prostaglandin analogs such as sulprostone.

Similar indications can be encountered in veterinary medicine for male or female domestic or wild animals that may require the use of pharmaceutical compositions according to the invention.

A further aspect of the invention relates to a method of treating and/or preventing the above diseases which comprises orally administering to patients or animals in need thereof a pharmaceutical composition according to the invention, said composition comprising an effective amount of a LH-RH peptide analogue as previously defined in combination with α-cyclodextrin or a derivative thereof. Said method may comprise the further administration of at least one of the active principles mentioned above such as for example a hormonal agent, an antitumoral agent, an immuno-modulating or -suppressive agent, a sex steroid, a gonadotrophin, an inhibitor of androgen action, a 5α-reductase inhibitor, a C_{17-20} lyase inhibitor, an antiestrogen, an aromatase inhibitor, a progestin, an estrogen, an antiprogestin or a prostaglandin analogue, said further administration being parallel, sequential or over a period of time.

The unit dose of oral administration of LH-RH peptide analogues according to formula (A) may range from 0.1 to 100 mg per human patient, from one to 16 times per day (in the case of pulsatile administration), in combination with at least an equimolar amount of α-CD or its derivatives and up to the total remaining part of the oral formulation.

All the above-mentioned oral pharmaceutical compositions may additionally contain one or several proteases inhibitors, and/or one or several other absorption enhancers.

Examples of preparations of leuprorelin, triptorelin, goserelin, deslorelin and examples 1 to 6 in combination with 100 mM α-CD in solution

On each experimental day, solutions of α-CD were freshly prepared by dissolving 9.72 g in 100 ml of pure water, or 4.86 g in 50 ml, for 1 hour at room temperature with gentle magnetic stirring; meanwhile, an appropriate volume of each LH-RH analogue was taken from thawed individual stock vials containing 50 μg of net peptide in 50 μl of phosphate-buffered saline containing 0.1% bovine serum albumin, to make 20 nmoles (24.2 μl for LEU, 26.2 μl for TRI, 23.4 μl for GOS, 25.4 μl for DES, 24.7 μl for example 1, 23.6 μl for example 2, 24.5 μl for example 3, 25.1 μl for example 4, 26.5 μl for example 5 and 23.4 μl for example 6) and put in a 10 ml gauged flask. Then, the α-CD solution was added to fill the flask up to 10 ml to make a 2 nmol/ml solution of which 1ml was administered by oral gavage to each rat.

Examples of preparation of formulations of example 2 in combination with 5%, 10% or 14% α-CD solutions

On each experimental day, 45 μl of one thawed individual vial containing 50 μg of net example 2 in 50 μl of phosphate-buffered saline containing 0.1 % bovine serum albumin, were diluted in 36 ml of distilled water to give a 1.25 μg/ml solution from which three fractions of 3.8 ml were taken; then, 190, 380 or 532 mg of α-CD were added to each fraction to give a concentration of 5%, 10% or 14%, respectively. After overnight magnetic stirring at room temperature, each solution was given to rats by oral gavage in a 4 ml/kg volume to administer the same dose of 5 μg/kg of example 2 without or with increasing concentrations of α-CD.

Examples of preparation of formulations for oral administration of example 3 in combination with α-CD derivatives

On each experimental day, frozen vials containing 50 μg of net example 3 in 50 μl of phosphate-buffered saline containing 0.1% bovine serum albumin were thawed and diluted by half with an equal volume of the same fresh bovine serum albumin solution. Then, 12.5 μl of this 0.5 μg/μl solution were added to 5 ml of aqueous vehicle for oral administration (with or without α-CD derivative) to give a

final formulation containing 1.25 μg/ml of example 3 to be administered by gavage under a volume of 4 ml/kg, after gentle magnetic stirring overnight.

The solutions of α-CD derivatives were prepared by weighing the appropriate amount to put in 10 ml gauged flasks to fill up with water : 5 g of carboxymethylated α-CD (50%), 3 g of methylated α-CD (30%), 3 g of phosphated α-CD (30%) or 1 or 1.5 g of permethylated α-CD (10 or 15%).

Appropriate volumes of convenient dilutions of the 50 μg/50 μl stock vials of net example 3 were added to 10% solutions of α-CD or permethylated α-CD in water to obtain the dose range described in figure 7.

Examples of preparations of formulations for oral administration of antide in combination with α-, β- or γ-CD

Each 5 mg powder vial of antide (from Bachem, Bubendorf, Switzerland) containing 4.2434 mg net peptide was dissolved in a mixture of 2.122 ml propylene glycol with 8.487 ml water containing 0.1% bovine albumin. To each 10.609 ml solution of antide (400 μg/ml), 1.061 g of either α-, β- or γ-CD was directly added to obtain a 10% concentration. Each female rat received the same volume of 1 ml of test formulation by gavage.

The same volume of administration was used for the doses of 200 and 600 μg/rat. The appropriate concentrations of antide to be administered (200 and 600 μg/ml) were respectively obtained by diluting by half the 400 μg/ml solution with the same [20% vol. propylene glycol/80% vol. albuminated water/10% wt α-CD] mixture, and by dissolving other 5 mg powder vials in 1.415 ml propylene glycol with 5.658 ml water already containing 0.1% bovine albumin to which 0.707 mg of α-CD was finally added.

CLAIMS

1. Use of α-cyclodextrin or a derivative thereof for the preparation of a pharmaceutical composition for the oral administration of a LH-RH peptide analogue or one of its pharmaceutically acceptable salt.

2. Use according to claim 1 wherein said peptide analogue has the formula (SEQ ID N° : 1) :

A1-A2-A3-A4-A5-A6-A7-A8-Pro-Z (A)

in which :

- A1 is pGlu ; D-pGlu ; Sar ; AcSar ; Pro or a derivative thereof ; Ser ; D-Ser ; Ac-D-Ser ; Thr ; D-Thr ; Ac-D-Thr ; or an optionally substituted and/or acylated aromatic D-amino acid;

- A2 is a direct bond ; His ; or an optionally substituted aromatic D-amino acid;

- A3 is an optionally substituted aromatic L- or D-amino acid;

- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;

- A5 is an optionally substituted aromatic L-amino acid or an optionally substituted basic L- or D-amino acid ;

- A6 is Gly ; (S)-spirolactam-Pro ; D-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Asn ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t) ; D-Ser(OR_1) where R_1 is a sugar moiety ; an aza-amino acid ; D-His which may be substituted on the imidazole ring by a (C_1-C_6)alkyl, a (C_2-C_7)acyl or a benzyl group ; an aliphatic D-amino acid with a (C_1-C_8)alkyl or a (C_3-C_6)cycloalkyl side chain ; an optionally substituted aromatic D-amino acid ; D-cyclohexadienyl-Gly ; D-perhydronaphthyl-Ala ; D-perhydrodiphenyl-Ala ; or an optionally substituted basic L- or D-amino acid;

- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C_1-C_4)alkyl group optionally substituted by one or several fluorine atoms ;

- A8 is an optionally substituted basic L- or D-amino acid;

- Z is GlyNH_2 ; D-AlaNH_2 ; azaGlyNH_2 ; or a group -NHR_2 where R_2 is a (C_1-C_4)alkyl which may be substituted by an hydroxy or one or several fluorine atoms ; a (C_3-C_6)cycloalkyl ; or a heterocyclic radical selected from morpholinyl, pyrrolidinyl and piperidyl.

3. Use according to claim 2 wherein said peptide analogue has the formula (SEQ ID N° : 2) :

A1-His-A3-A4-A5-A6-A7-A8-Pro-Z (I)

in which:

- A1 is pGlu, Sar or AcSar;
- A3 is an optionally substituted aromatic L-amino acid;
- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;
- A5 is an optionally substituted aromatic L-amino acid ;
- A6 is Gly ; D-Pro ; (S)-spirolactam-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t) ; D-Ser(OR$_1$) where R$_1$ is a sugar moiety ; an aza-amino acid ; D-His which may be substituted on the imidazole ring by a (C_1-C_6)alkyl or a benzyl group ; an aliphatic D-amino acid with a (C_1-C_8)alkyl or a (C_3-C_6)cycloalkyl side chain ; an optionally substituted aromatic D-amino acid ; D-cyclohexadienyl-Gly ; D-perhydronaphtyl-Ala ; D-perhydrodiphenyl-Ala ; or an optionally substituted basic D-amino acid;
- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C_1-C_4)alkyl group optionally substituted by one or several fluorine atoms;
- A8 is an optionally substituted basic L-amino acid;
- Z is GlyNH$_2$; azaGlyNH$_2$; or a group -NHR$_2$ where R$_2$ is a (C_1-C_4)alkyl which may be substituted by an hydroxy or one or several fluorine atoms ; a (C_3-C_6)cycloalkyl ; or a heterocyclic radical selected from morpholinyl, pyrrolidinyl and piperidyl.

4. Use according to claim 3 wherein said peptide analogue has the formula (SEQ ID N° : 3) :

pGlu-His-A3-Ser-A5-A6-A7-Arg-Pro-Z (II)

in which A7 is Leu, Tle, Nle, Hol, Npg, Cha or Ada, which may be N-alpha-substituted by a methyl or ethyl group optionally substituted by one or several fluorine atoms.

5. Use according to claim 3 wherein said peptide analogue has the formula (SEQ ID N° : 4) :

pGlu-His-A3-Ser-A5-A6-A7-Arg-Pro-Z (III)

in which:

- A3 and A5 are each independently Phe, Tyr, Trp, 2MeTrp, HPhe, HTyr, Nal, 1Nal, Bal, Pal, 4Pal, or pClPhe ;

- A6 is (S)-spirolactam-Pro ; Gly; D-Pro ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t); D-His or D-His(Bzl) ; D-Ala, D-Leu, D-Tle, D-Nle, D-Hol, D-Npg or D-Cha ; D-Phe, D-HPhe, D-Tyr, D-HTyr, D-Trp, D-2MeTrp, D-Nal, D-1Nal, D-Bal, D-Pal, D-4Pal, or D-pClPhe; D-cyclohexadienyl-Gly ; D-perhydronaphtyl-Ala ; D-perhydrodiphenyl-Ala ; or D-APhe optionally substituted by an aminotriazolyl group ;

- A7 is Leu, Npg or Cha, which may be N-alpha-substituted by a methyl group;

- Z is $GlyNH_2$; $azaGlyNH_2$ or $-NC_2H_5$.

6. Use according to claim 3 wherein said peptide analogue has the formula (SEQ ID N° : 5) :

pGlu-His-Trp-Ser-Tyr-A6-A7-Arg-Pro-Z (IV)

in which:

- A6 is (S)-spirolactam-Pro, D-Leu, D-Ala, D-Nal, D-Phe, D-Ser(OBu^t) or D-Trp;

- A7 is Leu, MeLeu, Npg or MeNpg;

- Z is $GlyNH_2$; $azaGlyNH_2$ or $-NC_2H_5$.

7. Use according to one of claims 3 to 6 wherein the peptide analogue is selected from the group consisting of leuprorelin, [Npg^7]-leuprorelin, triptorelin, [Npg^7]-triptorelin, goserelin, [Npg^7]-goserelin, buserelin and [Npg^7]-buserelin.

8. Use according to claim 2 wherein said peptide analogue has the formula (SEQ ID N° : 6) :

A1-A2-A3-A4-A5-A6-A7-A8-Pro-Z (I')

in which:

- A1 is pGlu ; D-pGlu ; Sar ; AcSar ; Pro or a derivative thereof ; Ser ; D-Ser ; Ac-D-Ser ; Thr ; D-Thr ; Ac-D-Thr ; or an optionally substituted and/or acylated aromatic D-amino acid;

- A2 is a direct bond or an optionally substituted aromatic D-amino acid;

- A3 is an optionally substituted aromatic L- or D-amino acid;

- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;

- A5 is an optionally substituted aromatic L-amino acid or an optionally substituted basic L- or D-amino acid;

- A6 is Gly ; (S)-spirolactam-Pro ; D-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Asn ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(O-Bu^t) ; D-Thr(O-Bu^t) ; D-Cys(O-Bu^t) ; D-Ser(O-R_1) where R_1 is a sugar moiety ; an aliphatic D-amino acid with a (C_1-C_8)alkyl or a (C_3-C_6)cycloalkyl side chain ; an optionally substituted aromatic D-amino acid ; D-cyclohexadienyl-Gly ; D-perhydronaphthyl-Ala ; D-perhydrodiphenyl-Ala ; or an optionally substituted basic L- or D-amino acid;

- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C_1-C_4)alkyl group optionally substituted by one or several fluorine atoms;

- A8 is an optionally substituted basic L- or D-amino acid;

- Z is GlyNH_2 or D-AlaNH_2.

9. Use according to claim 8 wherein the peptide analogue has the formula (SEQ ID N° : 7):

Ac-D-Nal-D-pClPhe-D-Pal-Ser-A5-A6-A7-A8-Pro-D-AlaNH_2 (II')

in which :

- A5 is Tyr, HTyr, MeTyr, MeHTyr, NicLys or IprLys;

- A6 is (S)-spirolactam-Pro, D-Arg, D-NicLys, D-IprLys, D-Cit, D-HCit or D-Asn;

- A7 is Leu, MeLeu, Npg or MeNpg;

- A8 is Arg, NicLys or IprLys.

10. Use according to claim 8 or 9 wherein the peptide analogue is selected from the group consisting of antide, [Npg^7]-antide, cetrorelix, [Npg^7]-cetrorelix, abarelix and [Npg^7]-abarelix.

11. Use according to one of claims 1 to 10 wherein the α-cyclodextrin derivative is selected from the group consisting of methylated α-cyclodextrin, hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin, carboxymethylated α-cyclodextrin and phosphated α-cyclodextrin.

12. Use according to one of claims 1 to 11 of α-cyclodextrin or hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin.

13. Use according to one of claims 1 to 12 wherein the pharmaceutical composition is intended to be delivered to the gastrointestinal tract.

14. Use according to one of claims 1 to 13 wherein the pharmaceutical composition is intended for the treatment of infertility, hypogonadic or hypergonadic states.

15. Use according to one of claims 1 to 13 wherein the pharmaceutical composition is a contraceptive agent.

16. Use according to one of claims 1 to 13 wherein the pharmaceutical composition is intended for the treatment or prevention of prostate cancer or benign prostatic hypertrophy.

17. Use according to one of claims 1 to 13 wherein the pharmaceutical composition is intended for the treatment or prevention of breast cancer.

18. Use according to one of claims 1 to 13 wherein the pharmaceutical composition is intended for the treatment or prevention of sex hormone-related benign or malignant tumors.

19. Use according to one of claims 1 to 13 wherein the pharmaceutical composition is intended for the treatment or prevention of sex hormone-independent but LH-RH sensitive benign or malignant tumors.

20. Use according to one of claims 1 to 13 wherein the pharmaceutical composition is intended for the treatment or prevention of benign or malignant lymphoproliferative disorders.

21. A pharmaceutical composition for the gastrointestinal delivery by oral administration of a LH-RH peptide analogue which comprises a therapeutically effective amount of said peptide analogue in combination with α-cyclodextrin or a derivative thereof.

22. The pharmaceutical composition according to claim 21 which further comprises excipients suitable for the gastrointestinal delivery of the peptide analogue.

23. The pharmaceutical composition according to claim 21 or 22 wherein said peptide analogue has the formula (SEQ ID N° : 1) :

A1-A2-A3-A4-A5-A6-A7-A8-Pro-Z (A)

in which :

- A1 is pGlu ; D-pGlu ; Sar ; AcSar ; Pro or a derivative thereof ; Ser ; D-Ser ; Ac-D-Ser ; Thr ; D-Thr ; Ac-D-Thr ; or an optionally substituted and/or acylated aromatic D-amino acid;

- A2 is a direct bond ; His ; or an optionally substituted aromatic D-amino acid;

- A3 is an optionally substituted aromatic L- or D-amino acid;

- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;

- A5 is an optionally substituted aromatic L-amino acid or an optionally substituted basic L- or D-amino acid;

- A6 is Gly ; (S)-spirolactam-Pro ; D-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Asn ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t) ; D-Ser(OR$_1$) where R$_1$ is a sugar moiety ; an aza-amino acid ; D-His which may be substituted on the imidazole ring by a (C_1-C_6)alkyl, a (C_2-C_7)acyl or a benzyl group ; an aliphatic D-amino acid with a (C_1-C_8)alkyl or a (C_3-C_6)cycloalkyl side chain ; an optionally substituted aromatic D-amino acid ; D-cyclohexadienyl-Gly ; D-perhydronaphthyl-Ala ; D-perhydrodiphenyl-Ala ; or an optionally substituted basic L- or D-amino acid;

- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C_1-C_4)alkyl group optionally substituted by one or several fluorine atoms;

- A8 is an optionally substituted basic L- or D-amino acid;

- Z is GlyNH$_2$; D-AlaNH$_2$; azaGlyNH$_2$; or a group -NHR$_2$ where R$_2$ is a (C_1-C_4)alkyl which may be substituted by an hydroxy or one or several fluorine atoms ; a (C_3-C_6)cycloalkyl ; or a heterocyclic radical selected from morpholinyl, pyrrolidinyl and piperidyl.

24. The pharmaceutical composition according to claim 23 wherein said peptide analogue has the formula (SEQ ID N° : 2) :

A1-His-A3-A4-A5-A6-A7-A8-Pro-Z (I)

in which:

- A1 is pGlu, Sar or AcSar;

- A3 is an optionally substituted aromatic L-amino acid ;

- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;

- A5 is an optionally substituted aromatic L-amino acid ;

- A6 is Gly ; D-Pro ; (S)-spirolactam-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t) ; D-Ser(OR$_1$) where R$_1$ is a sugar moiety ; an aza-amino acid ; D-His which may be substituted on the imidazole ring by a (C_1-C_6)alkyl or a benzyl group ; an aliphatic D-amino acid with a (C_1-C_8)alkyl or a (C_3-C_6)cycloalkyl side chain ; an optionally substituted aromatic D-amino acid ; D-cyclohexadienyl-Gly ;

D-perhydronaphtyl-Ala ; D-perhydrodiphenyl-Ala ; or an optionally substituted basic D-amino acid ;

- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C_1-C_4)alkyl group optionally substituted by one or several fluorine atoms;

- A8 is an optionally substituted basic L-amino acid;

- Z is $GlyNH_2$; $azaGlyNH_2$; or a group $-NHR_2$ where R_2 is a (C_1-C_4)alkyl which may be substituted by an hydroxy or one or several fluorine atoms ; a (C_3-C_6)cycloalkyl ; or a heterocyclic radical selected from morpholinyl, pyrrolidinyl and piperidyl.

25. The pharmaceutical composition according to claim 24 wherein said peptide analogue has the formula (SEQ ID N° : 3) :

pGlu-His-A3-Ser-A5-A6-A7-Arg-Pro-Z (II)

in which A7 is Leu, Tle, Nle, Hol, Npg, Cha or Ada, which may be N-alpha-substituted by a methyl or ethyl group optionally substituted by one or several fluorine atoms.

26. The pharmaceutical composition according to claim 24 wherein said peptide analogue has the formula (SEQ ID N° : 4) :

pGlu-His-A3-Ser-A5-A6-A7-Arg-Pro-Z (III)

in which:

- A3 and A5 are each independently Phe, Tyr, Trp, 2MeTrp, HPhe, HTyr, Nal, 1Nal, Bal, Pal, 4Pal, or pClPhe ;

- A6 is (S)-spirolactam-Pro ; Gly; D-Pro ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(OBu^t) ; D-Thr(OBu^t) ; D-Cys(OBu^t); D-His or D-His(Bzl) ; D-Ala, D-Leu, D-Tle, D-Nle, D-Hol, D-Npg or D-Cha ; D-Phe, D-HPhe, D-Tyr, D-HTyr, D-Trp, D-2MeTrp, D-Nal, D-1Nal, D-Bal, D-Pal, D-4Pal, or D-pClPhe; D-cyclohexadienyl-Gly ; D-perhydronaphtyl-Ala ; D-perhydrodiphenyl-Ala or D-APhe optionally substituted by an aminotriazolyl group;

- A7 is Leu, Npg or Cha, which may be N-alpha-substituted by a methyl group;

- Z is $GlyNH_2$, $azaGlyNH_2$ or $-NC_2H_5$.

27. The pharmaceutical composition according to claim 24 wherein said peptide analogue has the formula (SEQ ID N° : 5) :

pGlu-His-Trp-Ser-Tyr-A6-A7-Arg-Pro-Z (IV)

in which:

- A6 is (S)-spirolactam-Pro, D-Leu, D-Ala, D-Nal, D-Phe, D-Ser(OBu^t) or D-Trp;

- A7 is Leu, MeLeu, Npg or MeNpg;

- Z is GlyNH$_2$, azaGlyNH$_2$ or -NC$_2$H$_5$.

28. The pharmaceutical composition according to one of claims 24 to 27 wherein the peptide analogue is selected from the group consisting of leuprorelin, [Npg^7]-leuprorelin, triptorelin, [Npg^7]-triptorelin, goserelin, [Npg^7]-goserelin, buserelin and [Npg^7]-buserelin.

29. The pharmaceutical composition according to claim 23 wherein said peptide analogue has the formula (SEQ ID N° : 6) :

A1-A2-A3-A4-A5-A6-A7-A8-Pro-Z (I')

in which:

- A1 is pGlu ; D-pGlu ; Sar ; AcSar ; Pro or a derivative thereof ; Ser ; D-Ser ; Ac-D-Ser ; Thr ; D-Thr ; Ac-D-Thr ; or an optionally substituted and/or acylated aromatic D-amino acid;

- A2 is a direct bond or an optionally substituted aromatic D-amino acid;

- A3 is an optionally substituted aromatic L- or D-amino acid;

- A4 is Ala, Ser, D-Ser, MeSer, Ser(OBu^t), Ser(OBzl) or Thr;

- A5 is an optionally substituted aromatic L-amino acid or an optionally substituted basic L- or D-amino acid;

- A6 is Gly ; (S)-spirolactam-Pro ; D-Pro ; D-Ser ; D-Thr ; D-Cys ; D-Met ; D-Asn ; D-Pen ; D-(S-Me)Pen ; D-(S-Et)Pen ; D-Ser(OBu^t) ; D-Asp(OBu^t) ; D-Glu(O-Bu^t) ; D-Thr(O-Bu^t) ; D-Cys(O-Bu^t) ; D-Ser(O-R$_1$) where R$_1$ is a sugar moiety ; an aliphatic D-amino acid with a (C$_1$-C$_8$)alkyl or a (C$_3$-C$_6$)cycloalkyl side chain ; an optionally substituted aromatic D-amino acid ; D-cyclohexadienyl-Gly ; D-perhydronaphthyl-Ala ; D-perhydrodiphenyl-Ala ; or an optionally substituted basic L- or D-amino acid;

- A7 is a linear, branched or cyclic aliphatic L-amino acid of 3 to 20 carbon atoms which may be N-alpha-substituted by a (C$_1$-C$_4$)alkyl group optionally substituted by one or several fluorine atoms;

- A8 is an optionally substituted basic L- or D-amino acid;

- Z is GlyNH$_2$ or D-AlaNH$_2$.

30. The pharmaceutical composition according to claim 29 wherein the peptide analogue has the formula (SEQ ID N° : 7):

Ac-D-Nal-D-pClPhe-D-Pal-Ser-A5-A6-A7-A8-Pro-D-AlaNH$_2$ (II')

in which :

- A5 is Tyr, HTyr, MeTyr, MeHTyr, NicLys or IprLys;
- A6 is (S)-spirolactam-Pro, D-Arg, D-NicLys, D-IprLys, D-Cit, D-HCit or D-Asn;
- A7 is Leu, MeLeu, Npg or MeNpg;
- A8 is Arg, NicLys or IprLys.

31. The pharmaceutical composition according to claim 29 or 30 wherein the peptide analogue is selected from the group consisting of antide, [Npg^7]-antide, cetrorelix, [Npg^7]-cetrorelix, abarelix and [Npg^7]-abarelix.

32. The pharmaceutical composition according to one of claims 21 to 31 wherein the α-cyclodextrin derivative is selected from the group consisting of methylated α-cyclodextrin, hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin, carboxymethylated α-cyclodextrin and phosphated α-cyclodextrin.

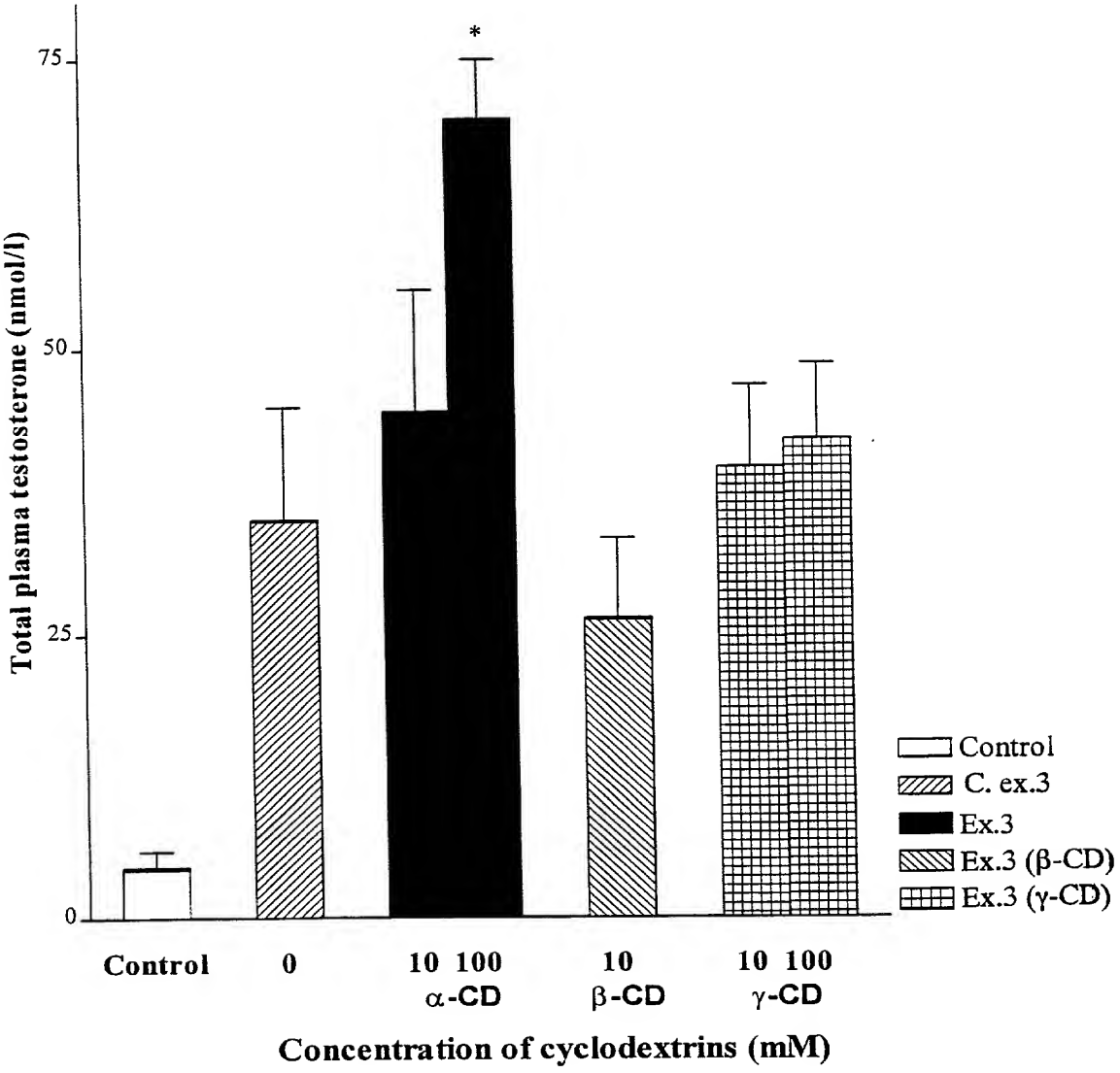
33. The pharmaceutical composition according to one of claims 21 to 32 comprising α-cyclodextrin or hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin in combination with the LH-RH peptide analogue.

34. The pharmaceutical composition according to one of claims 21 to 33 which further comprises a protease inhibitor and/or an absorption enhancer.

ABSTRACT

The invention relates to the use of α-cyclodextrin or a derivative thereof for the preparation of pharmaceutical compositions for the oral administration of LH-RH peptide analogues. The invention also relates to oral pharmaceutical compositions containing LH-RH peptide analogues in combination with α-cyclodextrin or a derivative thereof.

FIG.1



*p < 0.05 vs C. ex.3 in vehicle

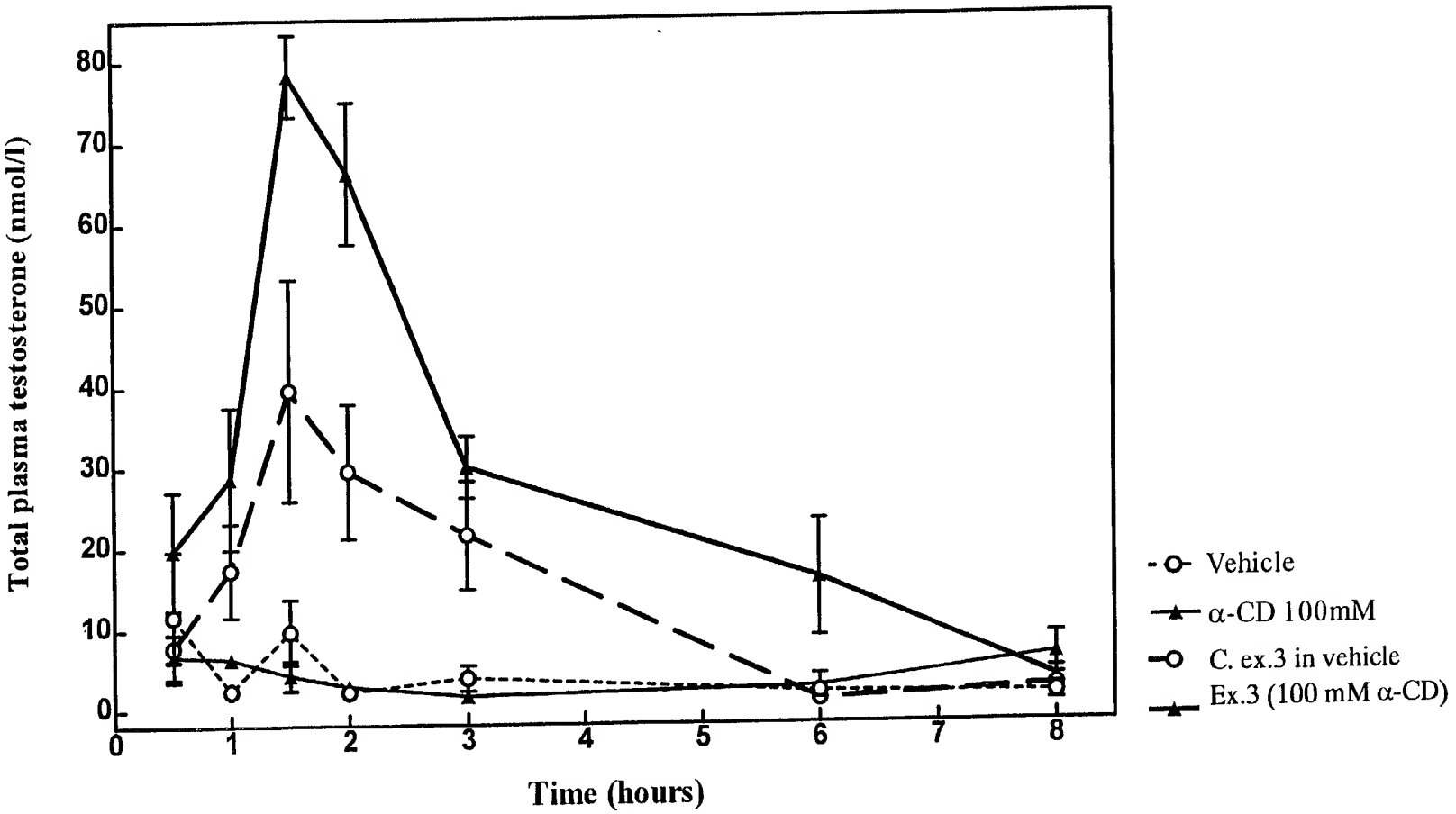


FIG. 2

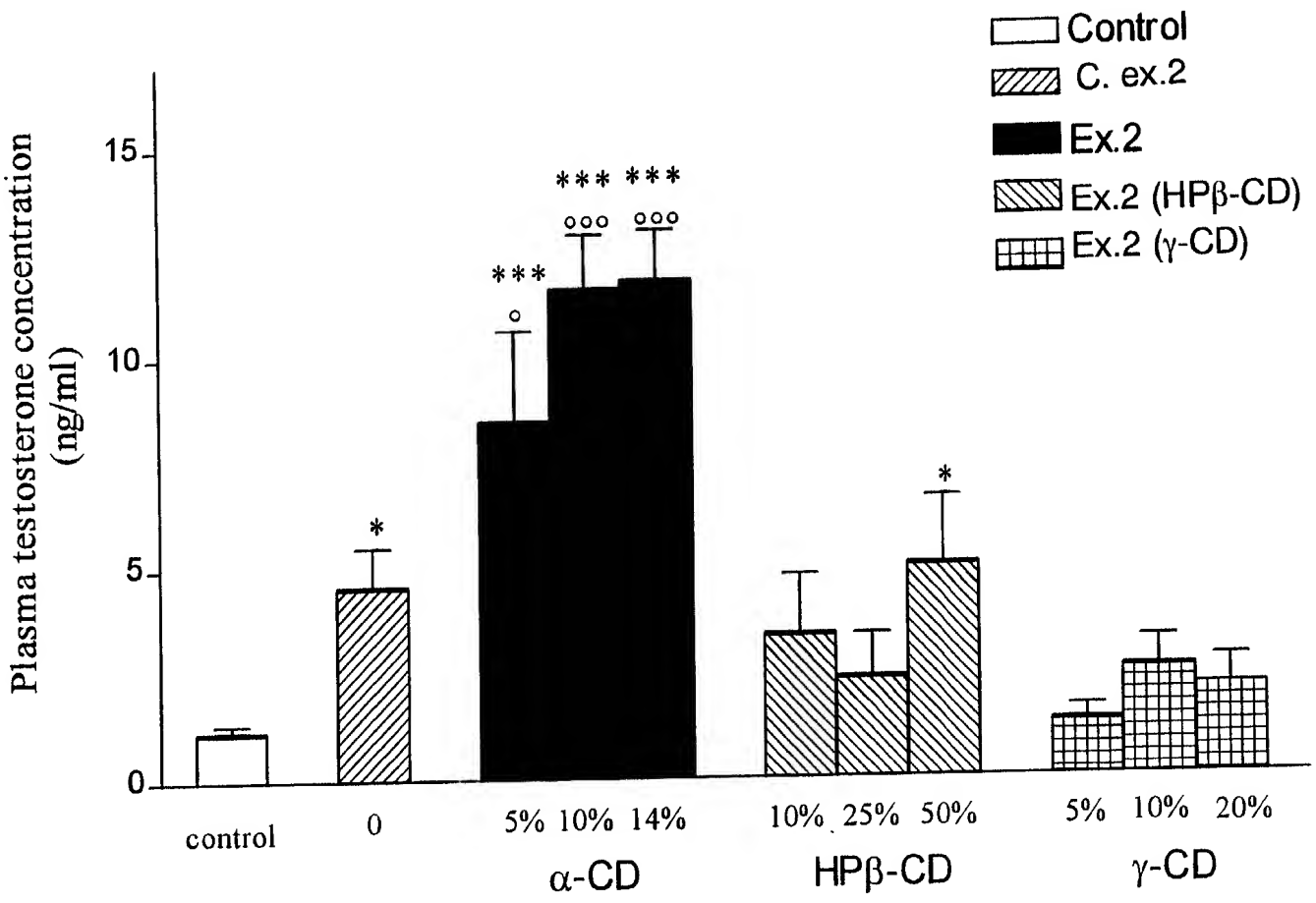


FIG.3

* $p<0.05$, *** $p<0.001$ vs control group
° $p<0.05$, °°° $p<0.001$ vs C. ex.2 in vehicle

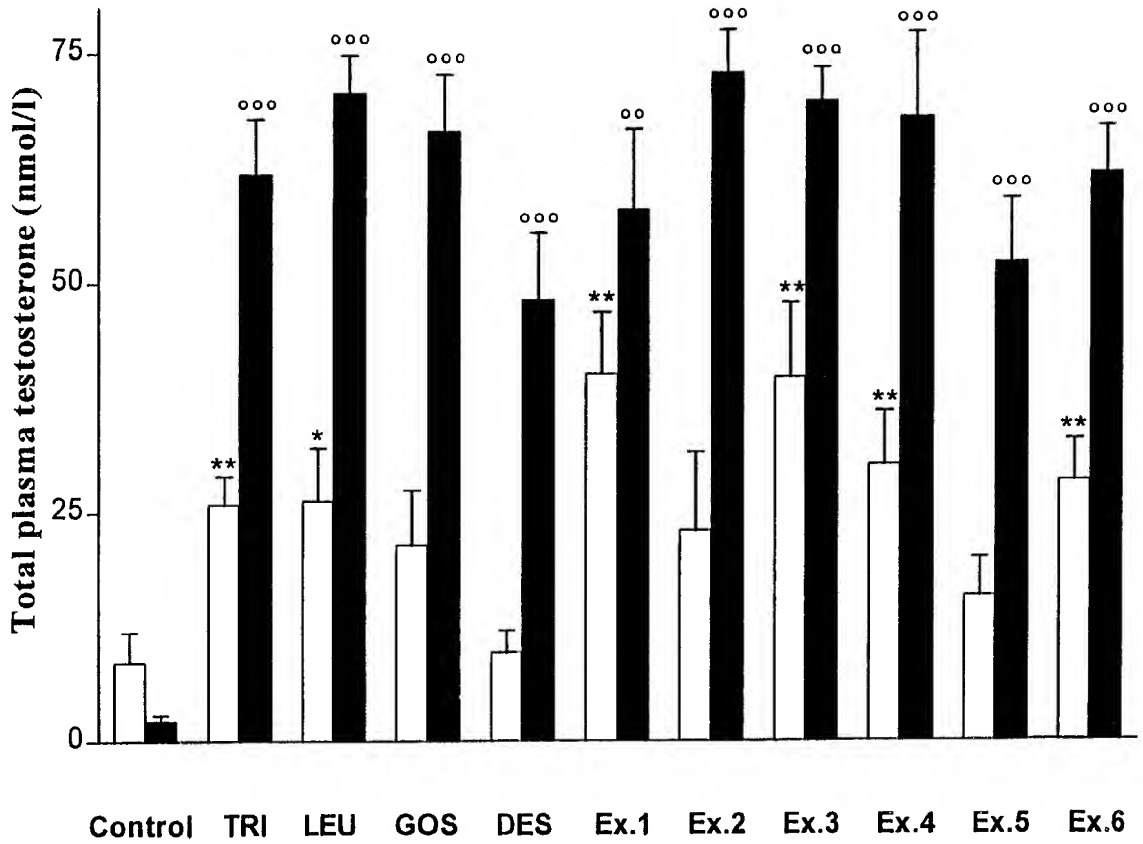


FIG.4

* p<0.05, **p<0.01 vs control without α-CD
°°p<0.01, °°°p<0.001 vs control α-CD

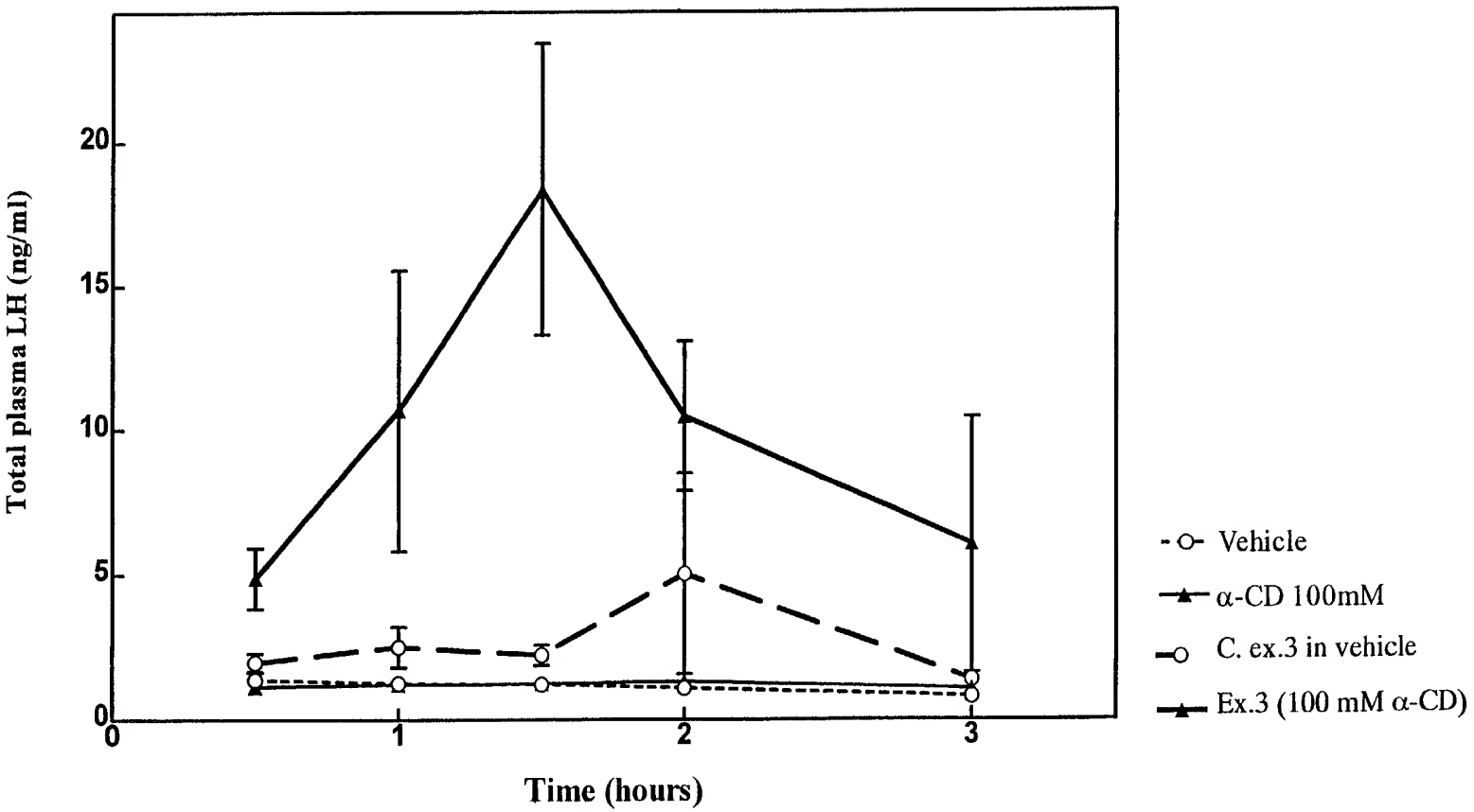


FIG.5

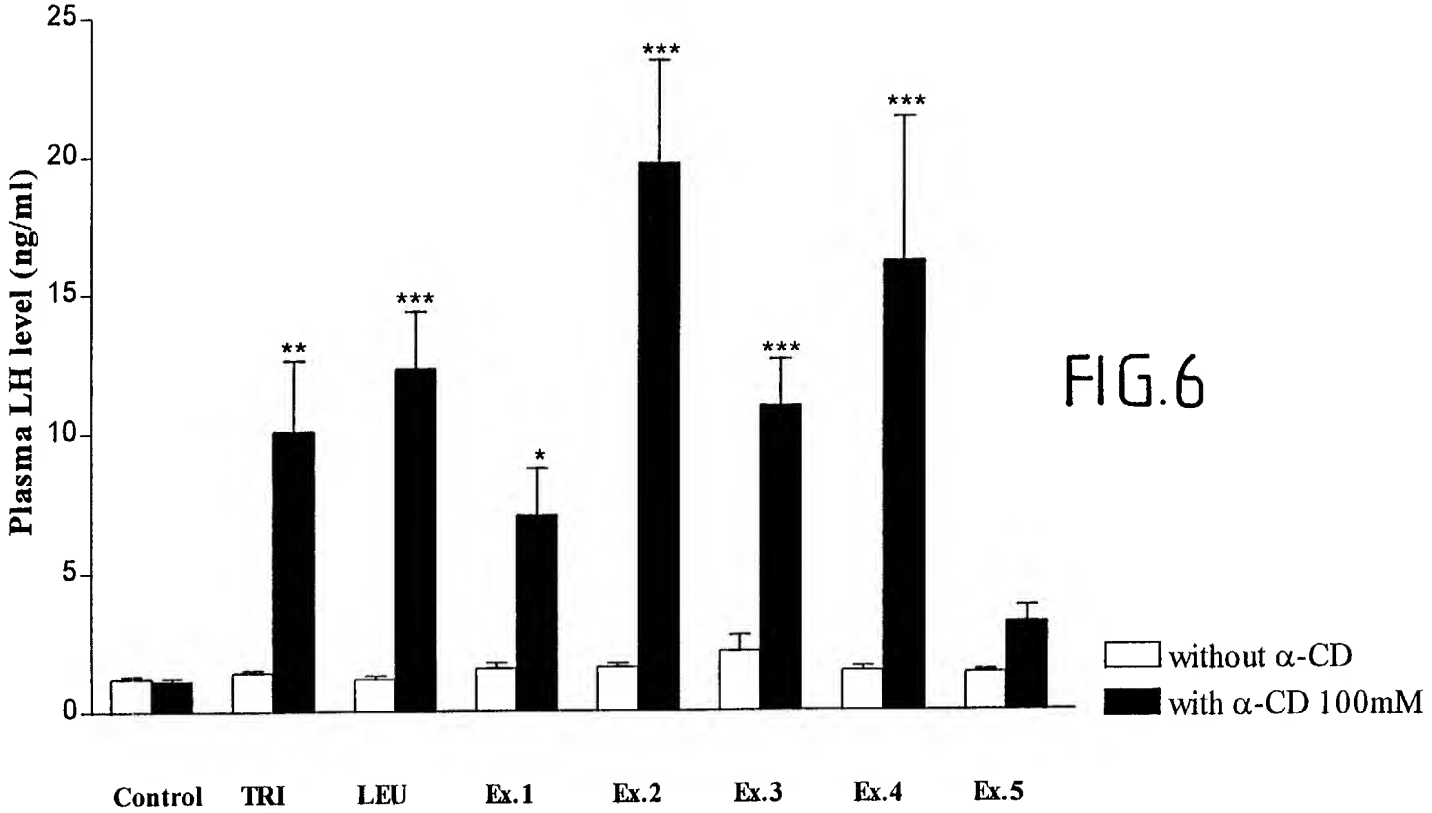
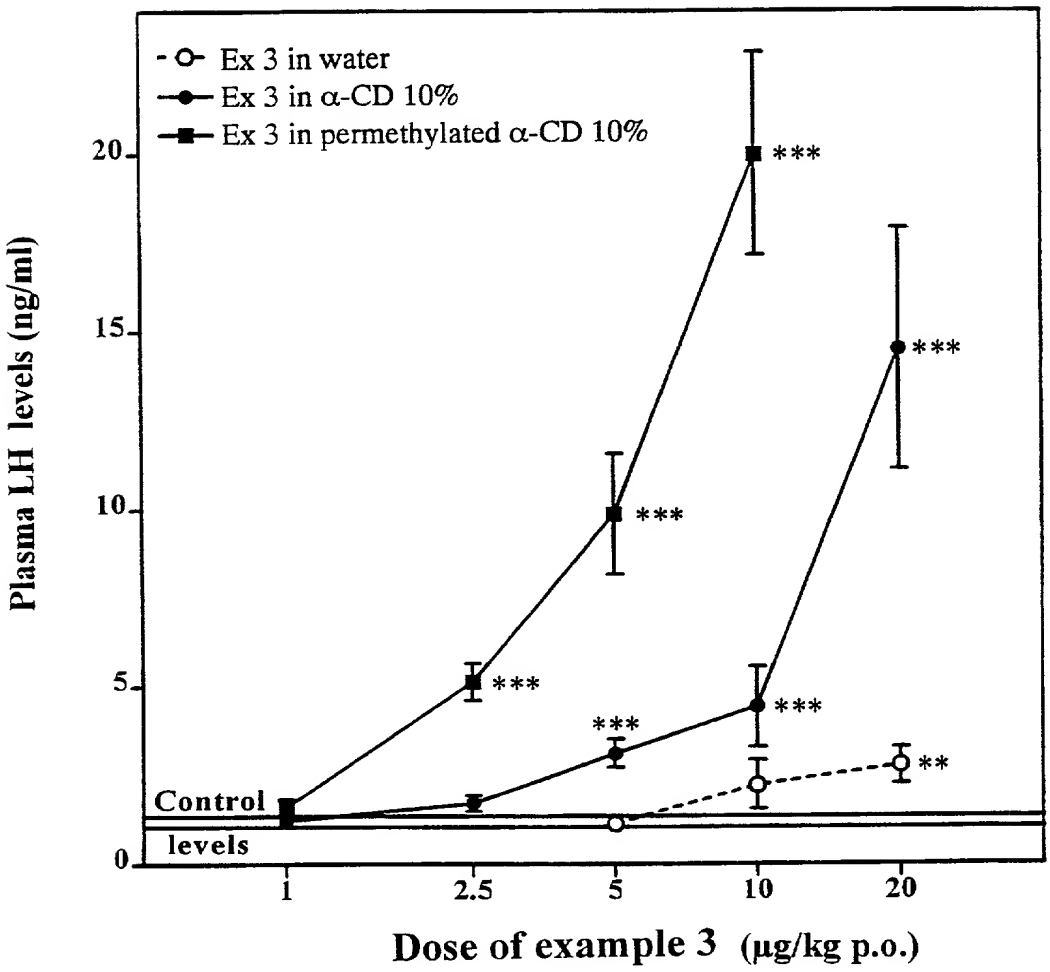


FIG.6

*p<0.05, **p<0.01, ***p<0.001 vs control α-CD

FIG.7



(**p<0.01;***p<0.001 vs. control unstimulated LH levels)

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Pharmaceutical compositions based on alpha-cyclodextrin for the oral administration of LH-RH analogues

the specification of which (check only one item below):

☐ is attached hereto.

☐ was filed as United States application

Serial No. _____

on _____,

and was amended

on _____ (if applicable).

☒ was filed as PCT international application

Number PCT/EP99/07389

on September 23, 1999,

and was amended under PCT Article 19

on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowlege the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
EP	98 402 403.4	30/09/1998	☒ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO

Combined Declaration For Patent Application and Power of Attorney (Continued)
(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowlege the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S APPLICATIONS		STATUS (Check one)		
U.S APPLICATION NUMBER	U.S FILING DATE	PATENTED	PENDING	ABANDONED

PCT APPLICATIONS DESIGNATING THE U.S					
PCT APPLICATION NO	PCT FILING DATE	U.S SERIAL NUMBERS ASSIGNED (if any)			

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(List name and registration number)* Donald L.Dennison, Reg.n° 19920, Burton Scheiner, Reg.n° 24018, Ira J.Schultz, Reg.n° 28666, Scott T.Wakeman, Reg.n° 37750

Send Correspondence to: Dennison, Scheiner, Schultz & Wakeman
1745 Jefferson Dais Highway, Suite 612
Arlington, Virginia 22202-3417

Direct Telephone Calls to: *(name and telephone number)*
(703) 412-1155

201	FULL NAME OF INVENTOR	FAMILY NAME: DELANSORNE	FIRST GIVEN NAME: Rémi	SECOND GIVEN NAME:
	RESIDENCE & CITIZENSHIP	CITY: NICE	STATE OR FOREIGN COUNTRY: France FAX	COUNTRY OF CITIZENSHIP: France
	POST OFFICE ADDRESS	POST OFFICE ADDRESS: 7bis Avenue Edith Cavell	CITY: 06000 NICE	STATE & ZIP CODE/COUNTRY: France
202	FULL NAME OF INVENTOR	FAMILY NAME: BONNET	FIRST GIVEN NAME: Paule	SECOND GIVEN NAME:
	RESIDENCE & CITIZENSHIP	CITY: MENTON	STATE OR FOREIGN COUNTRY: France FAX	COUNTRY OF CITIZENSHIP: France
	POST OFFICE ADDRESS	POST OFFICE ADDRESS: Villa "Rocailles" 37E Route de Sospel	CITY: 06500 MENTON	STATE & ZIP CODE/COUNTRY: France
203	FULL NAME OF INVENTOR	FAMILY NAME: PARIS	FIRST GIVEN NAME: Jacques	SECOND GIVEN NAME:
	RESIDENCE & CITIZENSHIP	CITY: NICE	STATE OR FOREIGN COUNTRY: France FAX	COUNTRY OF CITIZENSHIP: France
	POST OFFICE ADDRESS	POST OFFICE ADDRESS: 31 Avenue Cap de Croix-Bât E1	CITY: 06100 NICE	STATE & ZIP CODE/COUNTRY: France

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201	SIGNATURE OF INVENTOR 202	SIGNATURE OF INVENTOR 203
Rémi Delansorne	Paule BONNET	Jacques PARIS
DATE: March 13, 2001	DATE: March 13, 2001	DATE: March 13, 2001